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Today's t_ _nag_r exp_ cts a lot more than medicine from her doctor.

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The plight of today's teenager in these socially turbulent times is often precarious at best. According to a recent national survey, there has been a 30% increase in teenage sexual activity in the last five years.[1] Also, half of all out-of-wedlock births are attributed to teens. Up to two-thirds of these are unwanted, unplanned births.[2] Trapped in the midst of rapidly changing sexual mores, the teenager is further beset by uncertainty, timidity, ignorance, and misinformation.

That's why today's younger patient needs and deserves thorough counseling — underlined by compassion, reassurance, and trust — in many areas. These range from the basic facts of life, in some cases, to more serious subjects like venereal disease. But, no issue is more sensitive, or more in need of physician/patient exploration than that of contraception.

Today, contraceptive counseling often culminates in the selection of a low-dose oral contraceptive like Brevicon. Brevicon offers a rate of efficacy comparable to higher-dose formulations and its incidence of menstrual irregularities is low. In 16,345 cycles among 1,168 patients, there were 0.22 pregnancies per 100 woman years. Breakthrough bleeding occurred in 5.1% of cycles, and amenorrhea in 1.0% of cycles. Dropout rate due to menstrual irregularities during the crucial first three months was 3.4%.

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Brevicon® tablets **A sign of the times**

(norethindrone 0.5 mg with ethinyl estradiol 0.035 mg)

1. Zelnik, M. and Kantner, R.: Sexual and Contraceptive Experience of Young Married Women in the United States, 1976 and 1971. Family Planning Perspectives. Vol. 9, No. 2, March/April 1977.

2. Monthly Vital Statistics Report: Natality Statistics, National Center for Health Statistics, Vol. 26, No. 5, September 1977.

Note: Serious as well as minor side effects have been reported following the use of all oral contraceptives. These include thromboembolic disease. The physician should remain alert to the earliest manifestations of any symptoms of serious disease and discontinue oral contraceptive therapy when appropriate. The physician should be fully aware of the prescribing information for this product.

Please see following page for summary of prescribing information.

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ORAL CONTRACEPTIVE (O.C.) AGENTS

INDICATIONS O.C.s are indicated for the prevention of pregnancy. The drop-out rate for medical reasons, as observed in the clinical trials conducted with BREVICON, appears to be somewhat higher than observed with higher dose combination products. The dropout rate due to menstrual disorders and irregularities was also somewhat higher, dropouts being equally split between menstrual disorders and irregularities and other medical reasons attributable to the drug. *DOSE-RELATED RISK OF THROMBOEMBOLISM FROM O.C.s.* Studies have shown a positive association between the dose of estrogens in O.C.s and the risk of thromboembolism. For this reason, it is prudent and in keeping with good principles of therapeutics to minimize exposure to estrogen. The O.C. product prescribed for any given patient should be that product which contains the least amount of estrogen that is compatible with an acceptable pregnancy rate and patient acceptance. It is recommended that new acceptors of O.C.s should be started on preparations containing 0.05 mg or less of estrogen.

CONTRAINDICATIONS 1. Known or suspected pregnancy (see Warning No. 5). 2. O.C.s should not be used in women who have or have had any of the following conditions: a. Thrombophlebitis or thromboembolic disorders. b. Cerebral vascular or coronary artery disease. c. Markedly impaired liver function. d. Known or suspected carcinoma of the breast. e. Known or suspected estrogen dependent neoplasia. f. Undiagnosed abnormal genital bleeding.

WARNINGS: Cigarette smoking increases the risk of serious cardiovascular side effects from O.C. use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use O.C.s should be strongly advised not to smoke.

The use of O.C.s is associated with increased risk of several serious conditions including thromboembolism, stroke, myocardial infarction, liver tumor, gall bladder disease, visual disturbances, fetal abnormalities, and hypertension. Practitioners prescribing O.C.s should be familiar with the following information relating to these risks.

1. *Thromboembolic Disorders and Other Vascular Problems:* An increased risk of thromboembolic and thrombotic disease associated with the use of O.C.s is well established. One British study demonstrated an increased relative risk for fatal venous thromboembolism; two British and three American studies demonstrated an increased relative risk for non-fatal venous thromboembolism. These studies estimate that users of O.C.s are 4 to 11 times more likely than nonusers to develop these diseases without evident cause. CEREBROVASCULAR DISORDERS. Two American studies demonstrated an increased relative risk for stroke, which had not been shown in prior British studies. In a collaborative American study of cerebrovascular disorders in women with and without predisposing causes, it was estimated that the relative risk of hemorrhagic stroke was 2.0 times greater in users than nonusers and the relative risk of thrombotic stroke was 4 to 9.5 times greater in users than in nonusers. A British long-term, follow-up study reported in 1976 a highly significant association between O.C. use and stroke. Another British long-term, follow-up study had suggested such an association in 1974, but the number of cases was too small to estimate the risk. MYOCARDIAL INFARCTION. An increased relative risk of myocardial infarction associated with the use of O.C.s has been reported, confirming a previously suspected association. One study conducted in the United Kingdom found, as expected, that the greater the number of underlying risk factors for coronary artery disease (cigarette smoking, hypertension, hypercholesterolemia, obesity, diabetes, history of preeclamptic toxemia) the higher the risk of developing myocardial infarction, regardless of whether the patient was an O.C. user or not. O.C.s, however, were found to be an additional risk factor. In terms of relative risk, it has been estimated that O.C. users who do not smoke (smoking is considered a major predisposing condition to myocardial infarction) are about twice as likely to have a fatal myocardial infarction as nonusers who do not smoke. O.C. users who are also smokers have about a 5-fold increased risk of fatal infarction compared to users who do not smoke, and about a 10- to 12-fold increased risk compared to nonusers who do not smoke. Furthermore, the number of cigarettes smoked is also an important factor. In determining the importance of these relative risks, however, the baseline rates for various age groups must be given serious consideration. (The estimates are based on British vital statistics which show acute myocardial infarction death rates 2- to 3-times less than in the U.S. for women in these age groups; consequently, actual U.S. death rates could be higher.) The importance of other predisposing conditions mentioned above in determining relative and absolute risks has not been quantified; other synergistic actions may exist. RISK OF DOSE. In an analysis of data derived from several national adverse reaction reporting systems, British investigators concluded that the risk of thromboembolism including coronary thrombosis is directly related to the dose of estrogen used in O.C.s. Preparations containing 0.1 mg or more of estrogen were associated with a higher risk of thromboembolism than those containing 0.05-0.08 mg of estrogen. Their analysis did suggest, however, that the quantity of estrogen may not be the sole factor involved. This finding has been supported by a study in the United States. Careful epidemiological studies to determine the degree of thromboembolic risk associated with progestogen-only O.C.s have not been performed. Cases of thromboembolic disease have been reported in women using these products, and they should not be presumed to be free of excess risk. ESTIMATE OF EXCESS MORTALITY FROM CIRCULATORY DISEASE. A large British prospective study estimated the mortality rate per 100,000 women per year from diseases of the circulatory system for users and nonusers of O.C.s according to age, smoking habits, and duration of use. The overall excess death rate annually from circulatory diseases for O.C. users was estimated to be 20 per 100,000 (ages 15-34—5/100,000; ages 35-44—33/100,000; ages 45-49—140/100,000). The risk is concentrated in older women, in those with a long duration of use, and in cigarette smokers, and may persist after discontinuation of O.C. use. It was not possible, however, to examine the interrelationships of age, smoking, and duration of use, nor to compare the effects of continuous vs. intermittent use. Although the study showed a 10-fold increase in death due to circulatory diseases in users for 5 or more years, all of these deaths occurred in women 35 or older. Until larger numbers of women under 35 with continuous use for 5 or more years are available, it is not possible to assess the magnitude of the relative risk for this younger age group. The available data from a variety of sources have been analyzed to estimate the risk of death associated with various methods of contraception. The estimates of risk of death for each method include the combined risk of the contraceptive method (e.g., thromboembolic and thrombotic disease in the case of O.C.s) plus the risk attributable to pregnancy or abortion in the event of method failure. This latter risk varies with the effectiveness of the contraceptive method. The findings of this analysis are shown in Table 1 below. The study concluded that the mortality associated with all methods of birth control is low and below that of childbirth, with the exception of O.C.s in women over 40 who smoke. (The rates given for pill only/smokers for each age group are for smokers as a class. For "heavy" smokers (more than 15 cigarettes a day), the rates given would be about double; for "light" smokers (less than 15 cigarettes a day), about 50 percent.) The lowest mortality is associated with the condom or diaphragm backed up by early abortion. The study also concluded that O.C. users who smoke, especially those over the age of 30, have a greater mortality risk than O.C. users who do not smoke.

TABLE 1. *The annual number of deaths associated with control of fertility and no control per 100,000 nonsterile women by regimen of control and age of women are:*

	15-19	20-24	25-29	30-34	35-39	40-44
No method	5.6	6.1	7.4	13.9	20.8	22.6
Abortion only	1.2	1.6	1.8	1.7	1.9	1.2
Pill only—nonsmokers	1.3	1.4	1.4	2.2	4.5	7.1
Pill only—smokers	1.5	1.6	1.6	10.8	13.4	58.9
IUDs only	0.9	1.0	1.2	1.4	2.0	1.9
Traditional contraception only	1.1	1.6	2.0	3.6	5.0	4.2
Traditional contraception and abortion	0.2	0.2	0.3	0.3	0.3	0.2

The risk of thromboembolic and thrombotic disease associated with O.C.s is further increased by hypertension, hyperlipidemias, obesity, diabetes, or history of preeclampic toxemia and especially by cigarette smoking. Based on the data currently available, the following table gives a gross estimate of the risk of death from circulatory disorders associated with the use of O.C.s:

TABLE 2. *Smoking habits and other predisposing conditions – risk associated with use of O.C.s*

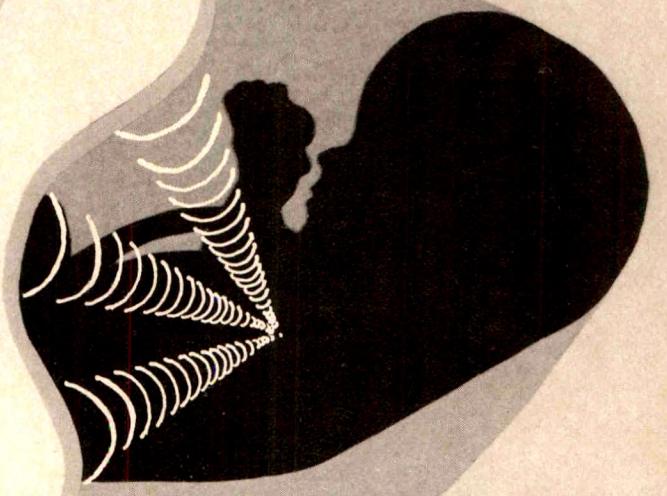
	Age	Below 30	30-39	40+
Heavy smokers		C	B	A
Light smokers		D	C	B
Nonsmokers (No predisposing conditions)		D	C,D	C
Nonsmokers (other predisposing conditions)		C	C,B	B,A

A—Use associated with very high risk. C—Use associated with moderate risk.
B—Use associated with high risk. D—Use associated with low risk.

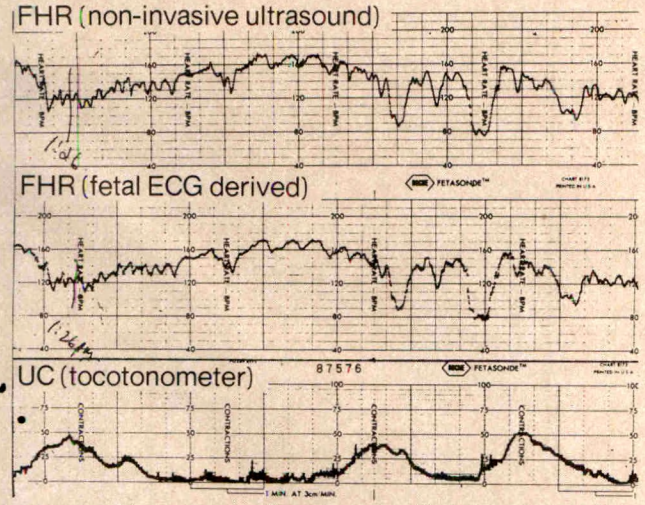
The physician and the patient should be alert to the earliest manifestations of thromboembolic and thrombotic disorders (e.g., thrombophlebitis, pulmonary embolism, cerebrovascular insufficiency, coronary occlusion, retinal thrombosis, and mesenteric thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately. A four- to six-fold increased risk of post-surgery thromboembolic complications has been reported in O.C. users. If feasible, O.C.s should be discontinued at least 4 weeks before surgery of a type associated with an increased risk of thromboembolism or prolonged immobilization. Among patients with thromboembolic disease, the results of retrospective studies suggest the possibility of an increased risk for users who are of blood types A, B, or AB, as compared with those of type O. *Ocular Lesions:* There have been reports of neuro-ocular lesions such as optic neuritis or retinal thrombosis associated with the use of O.C.s. Discontinue O.C. medication if there is unexplained, sudden or gradual, partial or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal vascular lesions; and institute appropriate diagnostic and therapeutic measures. *Carcinoma:* Long-term continuous administration of either natural or synthetic estrogen in certain animal species increases the frequency of certain adenomas, benign or malignant, such as those of the breast, cervix, vagina, uterus, ovary, pituitary and liver. Certain synthetic progestogens, none currently contained in O.C.s, have been noted to increase the incidence of mammary nodules, benign and malignant, in dogs. Several retrospective case-control studies have reported an increased relative risk (3.1 to 13.9 times) associating endometrial carcinoma with the prolonged use of estrogens in postmenopausal women who took estrogen replacement medication to relieve menopausal symptoms. One publication reported on the first 30 cases submitted by physicians to a registry of cases of adenocarcinoma of the endometrium in women under 40 on O.C s. Of the adenocarcinomas found in women without predisposing risk factors for adenocarcinoma of the endometrium (e.g., irregular bleeding at the time O.C.s were first given, polycystic ovaries) nearly all occurred in women who had used a sequential O.C. These products are no longer marketed. No statistical association has been reported suggesting an increased risk of endometrial cancer in users of conventional combination or progestogen-only O.C.s, although individual cases have been reported. Several studies have shown no increased risk of breast cancer to women taking O.C.s or estrogens. In one study, however, while no overall increased risk of breast cancer was noted in women treated with O.C.s, a greater risk was suggested for the subgroups of O.C. users with documented benign breast disease and for long-term (2-4 years) users. One other study indicated an increasing risk of breast cancer in women taking menopausal estrogens, which increased with duration of follow-up. A reduced occurrence of benign breast tumors in users of O.C.s has been well documented. In a prospective study of women with cervical dysplasia, there was an increase in severity and of conversion to cancer *in situ* in O.C. users compared with nonusers. This became statistically significant after 3 to 4 years of use. Nonreversal of dysplasia within the first 6 months of pill use was suggested to be predictive of progression after prolonged exposure. There have been other reports of microglandular hyperplasia of the cervix in users of O.C.s. In summary, there is at present no confirmed evidence from human studies of an increased risk of cancer associated with O.C.s. Close clinical surveillance of all women taking O.C.s is, nevertheless, essential. In all cases of undiagnosed persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be taken to rule out malignancy. Women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease or abnormal mammograms should be monitored with particular care if they elect to use O.C.s instead of other methods of contraception. 4. *Liver Tumors:* Sudden severe abdominal pain or shock may be due to rupture and hemorrhage of a liver tumor. There have been reports associating benign or malignant liver tumors with O.C. use. This has been reported in short-term as well as long-term users of O.C.s. One study showed that O.C. formulations with high hormonal potency were associated with a higher risk than lower potency formulations. Two studies relate risk with duration of use, the risk being much greater after 4 or more years of use. Although it is an uncommon lesion, it should be considered in women presenting with an "acute abdomen". The tumor may cause serious or fatal hemorrhage. Patients with liver tumors have demonstrated variable clinical features which may make preoperative diagnosis difficult. Some cases presented because of right upper quadrant masses, while most had signs and symptoms of acute intraperitoneal hemorrhage. Routine radiological and laboratory studies may not be helpful. Liver scans may clearly show a focal defect. Hepatic arteriography may be a useful procedure in diagnosing primary liver neoplasm. 5. *Use in or Immediately Preceding Pregnancy, Birth Defects in Offspring, and Malignancy in Female Offspring:* The use of female sex hormones—both estrogenic and progestational agents—during early pregnancy may seriously damage the offspring. It has been shown that females exposed *in utero* to diethylstilbestrol, a nonsteroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare. This risk has been estimated to be of the order of 1 in 1,000 exposures or less. Although there is no evidence at the present time that O.C.s further enhance the risk of developing this type of malignancy, such patients should be monitored with particular care if they elect to use O.C.s instead of other methods of contraception. Furthermore, a high percentage of women exposed to diethylstilbestrol (from 30 to 90%) have been found to have epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether this condition is a precursor of vaginal malignancy. Male children so exposed may develop abnormalities of the urogenital tract. Although similar data are not available with the use of other estrogens, it cannot be presumed that they would not induce similar changes. An increased risk of congenital anomalies, including heart defects and limb defects, has been reported following use of sex hormones, including O.C.s, in pregnancy. In one case-control study it was estimated that there was a 4.7-fold increased relative risk of limb-reduction defects in infants exposed *in utero* to sex hormones (O.C.s, hormonal withdrawal tests for pregnancy or attempted treatment for threatened abortion). Some of these exposures were very short and involved only a few days of treatment. The data suggest that the risk of limb-reduction defects in exposed fetuses is somewhat less than 1 in 1,000 live births. In a large prospective study, cardiovascular defects in children born to women who received female hormones, including O.C.s, during early pregnancy occurred at a rate of 18.2 per 1,000 births, compared to 7.8 per 1,000 for children not so exposed *in utero*. These results are statistically significant. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well controlled studies that progestogens are effective for these uses. There is some evidence that triploidy and possibly other types of polyploidy are increased among abortuses from women who become pregnant soon after ceasing O.C.s. Embryos with these anomalies are virtually always aborted spontaneously. Whether there is an overall increase in spontaneous abortion of pregnancies conceived soon after stopping O.C.s is unknown. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at the time of the first missed period (or after 45 days from the last menstrual period if progestogen-only O.C.s are used) and further use of O.C.s should be withheld until pregnancy has been ruled out. It is recommended that for any patient who has missed two consecutive periods, pregnancy should be ruled out before continuing the contraceptive regimen. If pregnancy is confirmed, the patient should be apprised of the potential risks to the fetus and the advisability of continuation of the pregnancy should be discussed in the light of these risks. It is also recommended that women who discontinue O.C.s with the intent of becoming pregnant use an alternate form of contraception for a period of time before attempting to conceive. Many clinicians recommend 3 months, although no precise information is available on which to base this recom-

combinations to induce withdrawal bleeding should not be used as a test o pregnancy. 6. *Gall Bladder Disease:* Studies found an increased risk of ga bladder disease in users of O.C.s or estrogens. In one study, an increase risk appeared after 2 years of use and doubled after 4 or 5 years of use. I another study an increased risk was apparent between 6 and 12 months o use. 7. *Carbohydrate and Lipid Metabolic Effects:* A decrease in glucose to erance has been observed in a significant percentage of patients on O.C.s For this reason, prediabetic and diabetic patients should be carefully ob served while receiving O.C.s. An increase in triglycerides and total phos pholipids has been observed in patients receiving O.C.s. The clinical signifi cance of this finding is unknown. 8. *Elevated Blood Pressure:* An increase in blood pressure has been reported with O.C. use. In some women, hyperten sion may occur within a few months of beginning O.C. use. In the first year o use, the prevalence of women with hypertension is low in users and may be no higher than that of a comparable group of nonusers. The prevalence in users increases, however, with longer exposure, and in the fifth year of use is two and a half to three times the reported prevalence in the first year. Age is also strongly correlated with the development of hypertension in O.C. users. Women with a history of elevated blood pressure (hypertension), preexisting renal disease, a history of toxemia or elevated blood pressure during preg nancy, a familial tendency to hypertension or its consequences, or a history of excessive weight gain or fluid retention during the menstrual cycle may be more likely to develop elevation of blood pressure when given O.C.s and therefore, should be monitored closely. Even though elevated blood pressur may remain within the "normal" range, the clinical implications of elevatio should not be ignored and close surveillance is indicated, particularly f women with other risk factors for cardiovascular disease or stroke. Hig blood pressure may or may not persist after discontinuation of the O.C. 9 *Headache:* The onset or exacerbation of migraine or development of headache of a new pattern which is recurrent, persistent, or severe, requires discon tinuation of O.C.s and evaluation of the cause. 10. *Bleeding Irregularities.* Breakthrough bleeding, spotting, and missed menses are frequent reasons for patients discontinuing O.C.s. In breakthrough bleeding, as in all cases of irregular bleeding from the vagina, nonfunctional causes should be borne in mind. In undiagnosed persistent or recurrent abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy. If pathology has been excluded, time or a change to another formulation may solve the problem. Changing to an O.C. with a higher estro gen content, while potentially useful in minimizing menstrual irregularity, should be done only if necessary since this may increase the risk of throm boembolic disease. Women with a past history of oligomenorrhea or secon dary amenorrhea or young women without regular cycles may have a tend ency to remain anovulatory or to become amenorrheic after discontinuation of O.C.s. Women with these preexisting problems should be advised of this possibility and encouraged to use other contraceptive methods. Post-use anovulation, possibly prolonged, may also occur in women without previous irregularities. A higher incidence of galactorrhea and of pituitary tumo (e.g., adenomas) has been associated with amenorrhea in former user compared with nonusers. One study reported a 16-fold increased prevalenc of pituitary prolactin-secreting tumors among patients with postpil amenorrhea when galactorrhea was present. 11. *Infertility:* There is evidence of impairment of fertility in women discontinuing O.C.s in comparison with those discontinuing other methods of contraception. The impairment appears to be independent of the duration of use of the preparations. While the in pairment diminishes with time, there is still an appreciable difference in th results in nulliparous women for the O.C. and non-O.C. groups 30 month after discontinuation of birth control. For parous women the difference is no longer apparent 30 months after cessation of contraception. 12. *Ectopic Pregnancy:* Ectopic as well as intrauterine pregnancy may occur in contracep tive failures. However, in progestogen-only O.C. failures, the ratio of ectopic to intrauterine pregnancies is higher than in women who are not receiving O.C.s, since the drugs are more effective in preventing intrauterine than ec topic pregnancies. 13. *Breast Feeding:* O.C.s given in the postpartum period may interfere with lactation. There may be a decrease in the quantity and quality of the breast milk. Furthermore, a small fraction of the hormonal agents in O.C.s has been identified in the milk of mothers receiving these drugs. The effects, if any, on the breast fed child have not been determined. If feasible, the use of O.C.s should be deferred until the infant has been weaned. **PRECAUTIONS** *GENERAL* 1. A complete medical and family history should be taken prior to the initiation of O.C.s. The pretreatment and periodic physical examinations should include special reference to blood pressure breasts, abdomen and pelvic organs, including Papanicolaou smear and re vant laboratory tests. As a general rule, O.C.s should not be prescribed fo longer than 1 year without another physical examination being performed. Under the influence of estrogen-progestogen preparations, preexistin uterine leiomyomata may increase in size. 3. Patients with a history psychic depression should be carefully observed and the drug discontinued depression recurs to a serious degree. Patients becoming significantly de pressed while taking O.C.s should stop the medication and use an alternate method of contraception in an attempt to determine whether the symptom is drug related. 4. O.C.s may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention, such as convulsive disorders, migraine syndrome, asthma or cardiac, hepatic or renal insufficiency. 5. Patients with a past history of jaundice during pregnancy have an increased risk of recurrence of jaundice while receiving O.C. therapy. If jaundice develops in any patient receiving such drugs, the medication should be discontinued. 6. Steroid hormones may be poorly metabolized in patients with impaired liver function and should be administered with caution in such patients. 7. O.C. users may have disturbances in normal tryptophan metabolism which may result in a relative pyridoxine deficiency. The clinical significance of this is unknown. 8. Serum folate levels may be depressed by O.C. therapy. Since the pregnant woman is predisposed to the development of folate deficiency and the incidence of folate deficiency increases with increasing gestation, it is possible that if a woman becomes pregnant shortly after stopping O.C.s, she may have a greater chance of developing folate deficiency and complications attributed to this deficiency. 9. The pathologist should be advised of O.C. therapy when relevant specimens are submitted. 10. Certain endocrine and liver function tests and blood components may be affected by estrogen-containing O.C.s. For example: a. Increased sulfobromophthalein retention. b. Increased prothrombin and factors VII, VIII, IX and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability. c. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG, free T4 concentration is unaltered. d. Decreased pregnanediol excretion. e. Reduced response to metyrapone test. *DRUG INTERACTIONS* O.C.s may be rendered less effective by virtue of drug interaction with rifampin, isoniazid, ampicillin, neomycin, penicillin V, chloramphenicol, sulfonamides, nitrofurantoin, barbiturates, phenytoin, primidone, analgesics, tranquilizers and antimigraine preparations. O.C.s may alter the effectiveness of other types of drugs, such as oral anticoagulants, anticonvulsants, tricyclic antidepressants, antihypertensive agents (e.g., quanethidine), vitamins and hypoglycemic agents. *CARCINOGENESIS* See Warnings. *PREGNANCY* Pregnancy category X. See Contraindications and Warnings. *NURSING MOTHERS* See Warnings. **ADVERSE REACTIONS** An increased risk of the following serious adverse reactions has been associated with the use of O.C.s (see Warnings): thrombophlebitis, thrombosis, pulmonary embolism, coronary thrombosis, cerebral thrombosis, mesenteric thrombosis, liver tumors, cerebral hemorrhage, hypertension, gall bladder disease, congenital anomalies, neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis. The following adverse reactions have been reported in patients receiving O.C.s and are believed to be drug related: bleeding irregularities (breakthrough bleeding, spotting, missed menses during treatment, amenorrhea after treatment), gastrointestinal symptoms (nausea, vomiting, bloating, abdominal cramps), dysmenorrhea, infertility after discontinuance of treatment, edema, chloasma or melasma which may persist after drug is discontinued, breast changes (tenderness, enlargement, and secretion), intolerance to contact lenses, change in corneal curvature (steepening) change in weight (increase or decrease), change in cervical erosion and cervical secretion, possible diminution in lactation when given immediately postpartum, cholestatic jaundice, migraine, increase in size of uterine leiomyomata, rash (allergic), mental depression, reduced tolerance to carbohydrates, vaginal candidiasis, prolactin-secreting pituitary tumors. The following adverse reactions have been reported in users of O.C.s, and the association has been neither confirmed nor refuted: premenstrual-like syndrome, cataracts, changes in libido, chorea, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, hirsutism, loss of hair, erythema multiforme, erythema nodosum, hemorrhagic eruption, vaginitis, porphyria, impaired renal function. **INFORMATION FOR THE PATIENT** (See Patient Package Insert)

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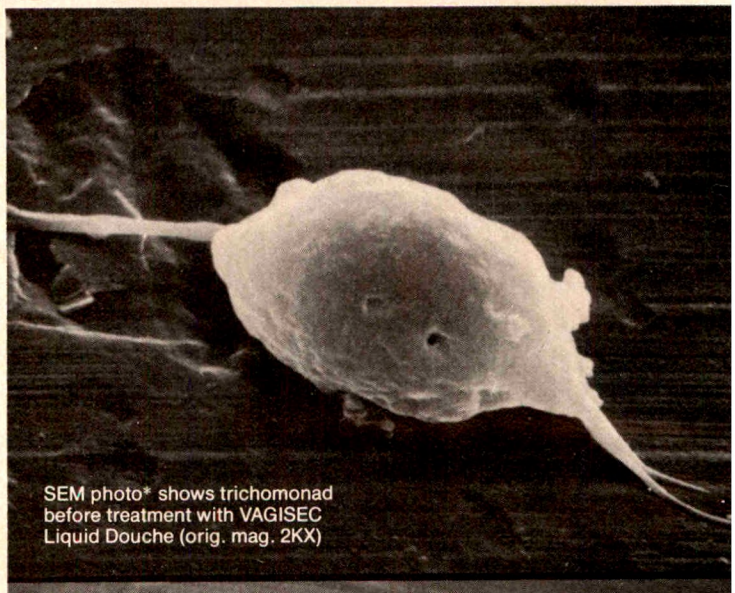
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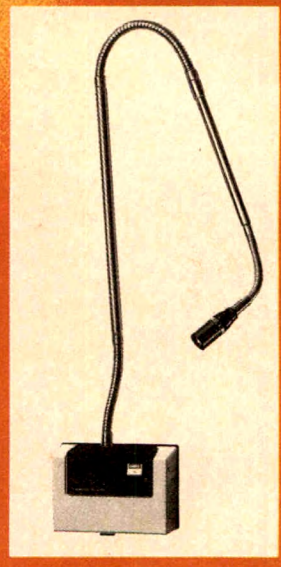
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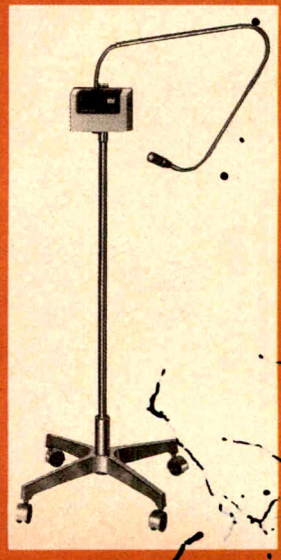
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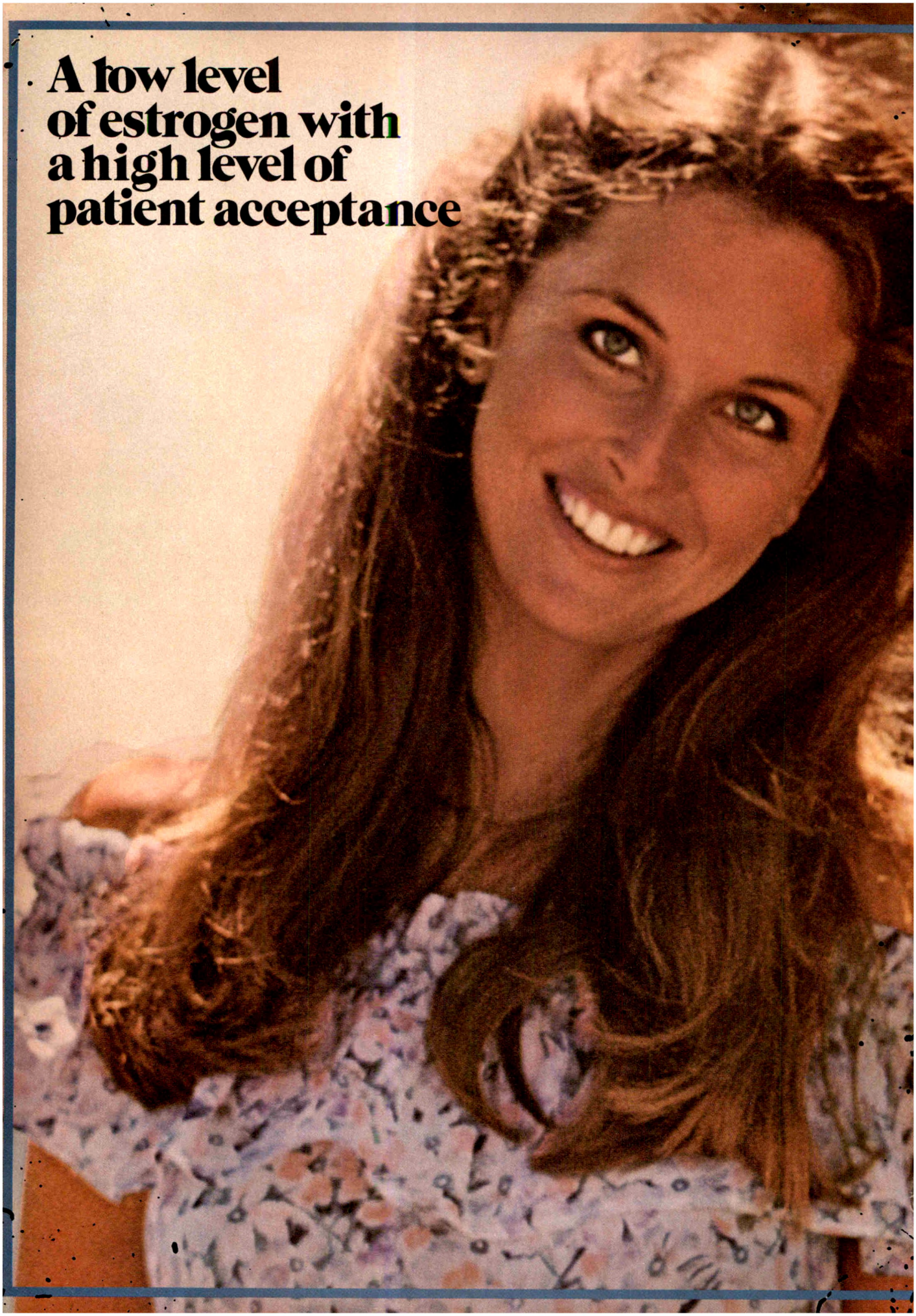
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Contraindications—Thrombophlebitis, thromboembolic disorders, cerebral vascular disease, myocardial infarction or coronary artery disease, or past history of these; known or suspected breast carcinoma, estrogen-dependent neoplasia, or pregnancy; undiagnosed abnormal vaginal bleeding; markedly impaired liver function; past or present, benign or malignant liver tumors.

Warnings

Cigarette-smoking increases risk of serious cardiovascular side effects from OC use. Risk increases with age and heavy smoking (15 or more cigarettes/day) and is quite marked in women over 35. OC users should be strongly advised not to smoke.

OCs are associated with increased risk of several serious conditions including venous and arterial thromboembolism, thrombotic and hemorrhagic stroke, myocardial infarction, visual disorders, hepatic tumors, gallbladder disease, hypertension, fetal abnormalities. Practitioners should be familiar with the available information relating to these and other risks.

1. Thromboembolic disorders and other vascular problems—Increased risk of thromboembolic and thrombotic disease associated with OCs is well established. A British study showed increased relative risk for fatal venous thromboembolism, 2 British and 3 U.S. studies increased relative risk for nonfatal venous thromboembolism. Two U.S. studies showed increased relative risk for stroke, not shown in prior British studies. It was estimated OC users were 2–11 times more likely than nonusers to manifest these diseases without evident cause. In a British study of idiopathic deep vein thrombosis and pulmonary embolism, projected hospitalization rates for ages 16-40 were 47/year/100,000 users and 5 for nonusers. In a British mortality study, overall excess mortality from pulmonary embolism or stroke was 1.3–3.4 deaths/year/100,000 users and increased with age. Cerebrovascular Disorders—In a U.S. study of stroke with and without predisposing causes, risk of hemorrhagic stroke was estimated as 2 times greater and thrombotic stroke 4.0–9.5 times greater in users. Mortality trends in 21 countries indicate that, since OC introduction, changes in mortality from nonrheumatic cardiovascular disease were associated with changes in the prevalence of OC use. The Royal College of GPs reported on its prospective study comparing users and nonusers: "A statistically significant higher rate of reporting of cerebrovascular accidents in Takers is evident, but the numbers are too small to justify an estimation of the degree of risk." They reported more superficial and deep vein thrombosis in users. A 1977 analysis showed a 5-fold increased mortality in users from circulatory diseases, mainly myocardial infarction (MI) and hemorrhagic stroke. Excess mortality was associated with age, smoking and duration of use. In 1976 a British Family Planning Association study found a highly significant association between OC use and stroke though total numbers were small; the increased risk for venous thrombosis and pulmonary embolism was about 4-fold and statistically highly significant. Circulatory disease mortality was significantly greater in users. Myocardial Infarction—An increased risk of MI associated with OC use was reported in Britain, as previously suspected. The morbidity study found the greater the number of risk factors for coronary artery disease (smoking, hypertension, hypercholesterolemia, obesity, diabetes, history of pre-eclamptic toxemia) the higher the MI risk, regardless of OC use. OCs were considered an additional risk factor. The excess rate of fatal MI in Britain was about 3.5/year/100,000 users aged 30–39 and 20 for ages 40–44. (These are based on British vital statistics with acute MI death rates 2–3 times less than the U.S. Similar estimates for U.S. are 25.7 for users aged 30–39 with predispositions vs. 1.5 without; for ages 40–44, 86.2 vs. 5.1.) Excess hospitalization rate for nonfatal MI in Britain was about 3.5/year/100,000 users aged 30–39 and 47 for ages 40–44. Smoking is a major predisposing condition to MI. In terms of relative risk, nonsmoking OC users are twice as likely to have fatal MI as nonsmoking nonusers. Smoking users have a 5-fold greater risk of fatal MI as nonsmoking users, but a 10–12-fold greater risk than nonsmoking nonusers. Amount of smoking is an important factor. In determining importance of these risks, give serious consideration to rates in table below. Importance of other predispositions cited above in determining relative and absolute risks has not been quantified; it is likely the same synergism exists, but perhaps to a lesser extent.

Estimated Mortality Rate from Myocardial Infarction per 100,000 Women/Year

	Aged 30–39		Aged 40–44	
	Users	Nonusers	Users	Nonusers
All smokers	10.2	2.6	62.0	15.9
≥15 cigarettes daily	13.0	5.1	78.7	31.3
<15 cigarettes daily	4.7	0.9	28.6	5.7
Nonsmokers	1.8	1.2	10.7	7.4
Smokers and nonsmokers	5.4	1.9	32.8	11.7

Risk of Dose—Reports of thromboembolism after use of OCs with ≥50 mcg. estrogen received by drug safety committees in Britain, Sweden and Denmark were compared with the distribution expected from market research sales estimates. A positive correlation was found between estrogen dose and reporting of thromboembolism, including coronary thrombosis, in excess of that predicted by sales. OCs with ≥100 mcg. estrogen were associated with higher thromboembolism risk than those with 50–80 mcg. The authors suggested that estrogen quantity may not be the sole factor. Any influence of progestogens was not considered, which may be responsible for certain discrepancies in the data. No significant differences were noted between OCs containing the same estrogen dose nor between ethinyl estradiol and mestranol. Studies on thromboembolic risk with progestogen-only OCs have not been done. Cases have been reported for these OCs and they are not presumed free of excess risk. In a U.S. case-controlled study, relative risk of OC use 1 month before hospitalization for various types of thromboembolism was calculated. If relative estrogenic potency and possible influence of different progestogens are ignored, OCs may be divided into those with <100 mcg. and those with ≥100 mcg. estrogen. For all cases combined, larger doses were associated with only slightly higher relative risk; for idiopathic cases relative risk was doubled with larger doses, but confidence limits overlapped and differences were not significant. Apparently there was no increased risk for cases with predispositions. Thromboembolic risk in users and nonusers increases with age. OCs have been considered an independent risk factor. Excess Mortality from Circulatory Diseases—A U.K. prospective study estimated annual mortality from circulatory diseases for OC users and nonusers according to age, smoking habits and duration of use. Excess mortality was 20/100,000 users (5 for ages 15–34, 33 for ages 35–44, 140 for ages 45–49), the risk being concentrated in older women, long-term users, and smokers. Interrelationships of age, smoking and duration of use could not be examined, nor could effects of continuous vs. intermittent use. Though circulatory mortality was increased 10-fold in users of >5 years, all deaths were in women over age 34. Until more under-35 users of 5+ continuous years are available, size of relative risk for this age group cannot be given. Risk of circulatory disease may have persisted after discontinuance of OCs. One study estimated risk of death with various contraceptive methods, each estimate including risk of method (e.g., thromboembolism for OCs) plus risk due to pregnancy or abortion in cases of method failure. This latter risk varies with effectiveness. It concluded mortality with all methods is low and below that of childbirth, except for OC users over 40 who smoke. Heavy smokers have double the risk of smokers as a class, light smokers about half. Mortality associated with OC use in nonsmokers over 40 is higher than with any other method in that age group. Lowest mortality is with the condom or diaphragm backed up by early legal abortion. Risk of thromboembolic and thrombotic disease associated with OCs increases with age after 30 and, for MI, is further increased by hypertension, hypercholesterolemia, obesity, diabetes, history of pre-eclamptic toxemia, and especially cigarette smoking. Based on current data, the chart gives gross estimates of risk of death from circulatory disorders associated with OCs:

Risk is: A—very high, B—high, C—moderate, D—low. Age:	<30	30–39	≥40
Heavy smokers (≥15/day)	C	B	A
Light smokers (<15/day)	D	C	B
Nonsmokers, no predispositions	D	C,D	C
Nonsmokers, with predispositions	C	C,B	B,A

Physician and patient should be alert to earliest manifestations of thromboembolic and thrombotic disorders (e.g., thrombophlebitis, pulmonary embolism, cerebrovascular insufficiency, coronary artery disease, myocardial infarction, retinal thrombosis, mesenteric thrombosis). Should any of these occur or be suspected, discontinue OCs immediately. A 4–7-fold increased risk of postsurgery thromboembolism was reported in users; if feasible discontinue OCs at least 4 weeks before elective surgery or during prolonged immobilization and do not resume until at least 4 weeks postsurgery. Thromboembolic risk may be increased for users with blood types A, B or AB. 2. Ocular lesions—Neuro-ocular lesions such as optic neuritis or retinal thrombosis have been associated with OCs. Discontinue if there is unexplained, gradual or sudden, partial or complete loss of vision; proptosis or diplopia; papilledema; or evidence of retinal vascular lesions. Institute diagnostic and therapeutic measures. 3. Carcinoma—Long-term estrogen in certain animals increases carcinomas such as those of breast, uterus, cervix, vagina, ovary, liver, pituitary. Some synthetic progestogens, none currently in OCs, increase incidence of benign and malignant mammary nodules in dogs. There is no evidence that estrogens increase risk of human endometrial carcinoma. In several case-controlled studies increased relative risk (3.1–13.9 times) associated endometrial carcinoma with prolonged estrogen for menopausal symptoms. Risk was independent of other known risk factors and depended on duration of use and dose. This is supported by increased endometrial cancer incidence since 1969 in 8 U.S. areas with cancer-reporting systems, which may be related to rapidly expanding estrogen use. There is no evidence that natural estrogens are more or less hazardous than synthetics at equi-estrogenic doses. Of the first 30 cases of endometrial carcinoma in OC users under 40, those without predispositions (e.g., irregular bleeding before OCs, polycystic ovaries) occurred nearly always with no-longer-marketed sequential OCs. No statistical association is reported suggesting increased endometrial cancer with combination or progestogen-only OCs, though individual cases have been reported. Studies show no increased breast cancer with OCs or estrogens. However, greater risk was noted in OC users with benign breast disease or long-term (2–4 years) use. Risk of breast cancer with menopausal estrogens rose and further increased with duration of follow-up. Decreased benign breast tumors in OC users is well known. Some studies suggested increased risk of cervical dysplasia, erosion and carcinoma in long-term users; cause and effect is not established. Cervical microglandular hyperplasia has been reported. In summary, there is no confirmed evidence from human studies of increased cancer risk with OCs. Close surveillance is, however, essential. In undiagnosed persistent or recurrent abnormal vaginal bleeding, consider nonfunctional causes and take appropriate diagnostic measures to rule out malignancy. Carefully monitor users with a strong family history of breast cancer or with breast nodules, fibrocystic disease, recurrent cystic mastitis, abnormal mammograms, or cervical dysplasia. 4. Hepatic adenomas, hepatomas, hamartomas, regenerating nodules, focal nodular hyperplasia, hemangiomas, hepatocellular carcinoma, etc. have been associated with OCs. In 1 study OC formulations with high "hormonal potency" were associated with higher risk. Though benign these hepatic lesions may rupture and cause fatal hemoperitoneum in short- or long-term users. Two studies related risk to duration of use, being much greater after ≥4 years. Consider such lesions in users with abdominal pain, tenderness, mass or shock. About 25% present with abdominal masses; up to half with acute hemoperitoneum. Routine radiologic and lab studies may not be helpful; liver scans may show a focal defect. Hepatic arteriography or CAT may be useful in diagnosis. Hepatocellular carcinoma was noted in a few users. OCs are contraindicated in case of past or present, benign or malignant liver tumors. 5. Use in or immediately preceding pregnancy, birth defects, malignancy in offspring—Estrogens or progestogens during early pregnancy may seriously damage offspring. Females exposed in utero to DES and other nonsteroidal estrogens may have increased risk of vaginal or cervical cancer. Though OCs may not enhance this risk, monitor such patients carefully. From 30–90% of DES-exposed women develop benign vaginal or cervical adenosis, which could be premalignant. Males so exposed may develop urogenital defects. Other estrogens may mimic DES. Reports relate fetal exposure to female sex hormones and congenital anomalies, e.g., multiple anomalies described by VACTERL for vertebral, anal, cardiac, tracheoesophageal, renal and limb defects. There appears preferential expression by males. There was a 4.7-fold increased risk of limb-reduction defects in infants exposed in utero to sex hormones (OCs, hormonal withdrawal pregnancy tests or treatment for threatened abortion). Some exposures were very short, being only a few days. Cardiovascular defects in children exposed to female hormones, including OCs, during early pregnancy occurred at 18.2/1000 births, compared to 7.8 for those unexposed (P<.05). Female sex hormones were used for threatened or habitual abortion, but there is considerable evidence estrogens are ineffective and no evidence progestogens are effective. Triploidy and possibly other polyploidy may be increased in abortuses from women becoming pregnant soon post-OC. These almost always abort spontaneously. It is unknown if spontaneous abortion is increased soon after stopping OCs. Safety of OCs in pregnancy has not been demonstrated. Rule out pregnancy in using OCs and always consider it if withdrawal bleeding does not occur. If 2 consecutive periods are missed rule out pregnancy before continuing. If user deviates from regimen, consider pregnancy at first missed period and withhold OCs. If pregnancy is confirmed, apprise patient of potential fetal risks and discuss continuation of pregnancy. Users discontinuing for pregnancy should use alternative contraception for 3 months before attempting to conceive, though this is not based on precise information. Do not use progestogen-only or progestogen-estrogen drugs as pregnancy tests. 6. Gallbladder disease risk, surgically confirmed, appeared after 2 years' use and doubled after 4–5 years in 1 study; it appeared in 6–12 months' use in another. 7. Carbohydrate & lipid metabolism—Decreased glucose tolerance occurs in a significant number of users; carefully observe diabetic and prediabetic patients. Triglycerides and total phospholipids may increase. 8. Elevated blood pressure (BP) occurs in some users in a few months, and degree may relate to progestogen dose. Hypertension prevalence in users is no higher than in nonusers in the first year, but increases with longer exposure; in the 5th year it is 2½–3 times the first year. Age is strongly correlated with hypertension in users. Those with history of elevated BP (hypertension), pre-existing renal disease, history of toxemia or elevated BP in pregnancy, familial tendency to hypertension or its consequences, or history of excessive weight gain or fluid retention during menstrual cycles may be more likely to develop elevated BP on OCs and thus should be monitored closely. Even though elevated BP may be in the "normal" range, do not ignore clinical implications. Follow closely, particularly those with other risk factors for cardiovascular disease or stroke. High BP may or may not persist after stopping OCs. 9. Headache—Onset or exacerbation of migraine or development of headache of a new pattern that is recurrent, persistent or severe requires stopping OCs and evaluating cause. 10. Bleeding irregularities—Breakthrough bleeding (BTB), spotting and amenorrhea are frequent reasons for discontinuing. In BTB, as in all cases of irregular bleeding, consider nonfunctional causes. In undiagnosed persistent or recurrent bleeding, rule out pregnancy or malignancy. If pathology is excluded, time or change to another product may suffice. Change to a higher estrogen OC only when necessary as this may increase thromboembolic risk. Those with a history of oligomenorrhea or secondary amenorrhea or without established regular cycles may be anovulatory or amenorrheic after discontinuing. Those with such problems should be so informed and other methods encouraged. Post-use anovulation, possibly prolonged, may occur in women without previous irregularities. Higher incidence of galactorrhea and of pituitary tumors (e.g., adenomas) has been associated with postpill amenorrhea. One study reported 16-fold increased prevalence of pituitary prolactin-secreting tumors in patients with postpill amenorrhea when galactorrhea was present. 11. Ectopics—In failures with combination OCs, the ratio of ectopic to intrauterine pregnancies is no higher than in nonusers. There may be an increased risk of ectopics after discontinuing. 12. Breast feeding—OCs may decrease quantity and quality of milk. A small fraction of OC steroids appears in milk. Effects if any on the child are unknown. If feasible defer OCs until after weaning. 13. Infertility may occur in women discontinuing OCs, which appears independent of duration of use. While impairment diminishes with time, there is still an appreciable difference in nulliparous but not parous women after 30 months; difference is negligible after 42 months.

Precautions—Conduct complete history and physical prior to OC use and annually thereafter. Include breasts, abdomen and pelvis, with BP, pap and lab tests. Pre-existing uterine leiomyomata may enlarge. Mental depression may occur; with positive history, observe carefully and discontinue if serious recurrence. Fluid retention may occur; prescribe cautiously and monitor carefully in convulsive disorders, migraine, asthma, or cardiac, hepatic or renal dysfunction. History of jaundice in pregnancy increases risk of recurrence on OCs; observe carefully and discontinue if jaundice occurs. Steroids may be poorly metabolized in liver dysfunction and should be given cautiously. Tryptophan metabolism may be disturbed and result in pyridoxine deficiency; megaloblastic anemia has been reported. Serum folate may be depressed and may be exacerbated in post-OC pregnancy. Advise pathologist of OC use when submitting specimens. Endocrine and liver function tests may be altered; repeat abnormal tests after stopping for 2 months. These have been observed: increased BSP retention and other abnormalities in liver function tests; increased prothrombin and coagulation factors VII, VIII, IX, X; decreased antithrombin III, increased platelet aggregability; increased thyroid-binding globulin leading to increased circulating total thyroid hormone (PBI, T_4); decreased T_3 uptake, unaltered free T_4; decreased pregnanediol excretion; reduced metyrapone response; increased blood transcortin, corticosteroid, triglyceride, phospholipid; reduced serum folate; impaired glucose tolerance; altered plasma trace minerals. Influence of prolonged OC use on pituitary, ovarian, adrenal, hepatic, or uterine function, or on immune response is not established. OCs may mask onset of climacteric. Information for patients—see patient labeling. Drug interactions—OC effectiveness may be decreased and more BTB occur with rifampicin, isoniazid, ampicillin, neomycin, penicillin V, chloramphenicol, sulfonamides, nitrofurantoin, barbiturates, phenytoin, primidone, phenylbutazone, analgesics, tranquilizers, antimigraines. OCs may alter effectiveness of drugs such as oral anticoagulants, anticonvulsants, tricyclic antidepressants, antihypertensives, vitamins, hypoglycemics.

Adverse Reactions—Increased risk of the following serious adverse reactions has been associated with OCs: thrombophlebitis and thrombosis; pulmonary embolism; myocardial infarction and coronary thrombosis; cerebral thrombosis; cerebral hemorrhage; hypertension; gallbladder disease; benign adenomas and other hepatic lesions, with or without intra-abdominal bleeding; congenital abnormalities. There is evidence of association between the following conditions and OCs, though confirmatory studies have not been done: mesenteric thrombosis; Budd-Chiari syndrome, neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis. The following have been reported with OCs and are believed drug related: nausea, vomiting, gastrointestinal symptoms, breakthrough bleeding, spotting, change in menstrual flow, dysmenorrhea, amenorrhea during and after use, infertility post-OC, edema, chloasma or melasma, which may persist post-OC, breast changes (tenderness, enlargement, secretion), weight changes, change in cervical erosion and secretion, endocervical hyperplasia, lactation decrease, cholestatic jaundice, migraine, enlarged uterine leiomyomata, allergic rash, mental depression, reduced carbohydrate tolerance, vaginal candidiasis, change in corneal curvature (steepening), intolerance to contact lenses. The following have been reported and association has not been confirmed or refuted: premenstrual-like syndrome, cataracts, libido changes, chorea, appetite changes, cystitis-like syndrome, headache, paresthesia, nervousness, dizziness, auditory disturbances, rhinitis, fatigue, backache, hirsutism, scalp hair loss, erythema multiforme or nodosum, hemorrhagic eruption, itching, vaginitis, porphyria, impaired renal function, anemia, pancreatitis, hepatitis, colitis, gingivitis, lupus erythematosus, rheumatoid arthritis, pituitary tumors (e.g., adenoma) with amenorrhea and/or galactorrhea after use, endometrial, cervical and breast carcinoma.

Acute overdosage—Serious ill effects have not been reported after large acute doses of OCs in young children, but nausea and withdrawal bleeding might occur.

Important note—Full prescribing information should be consulted prior to use and is available on request.

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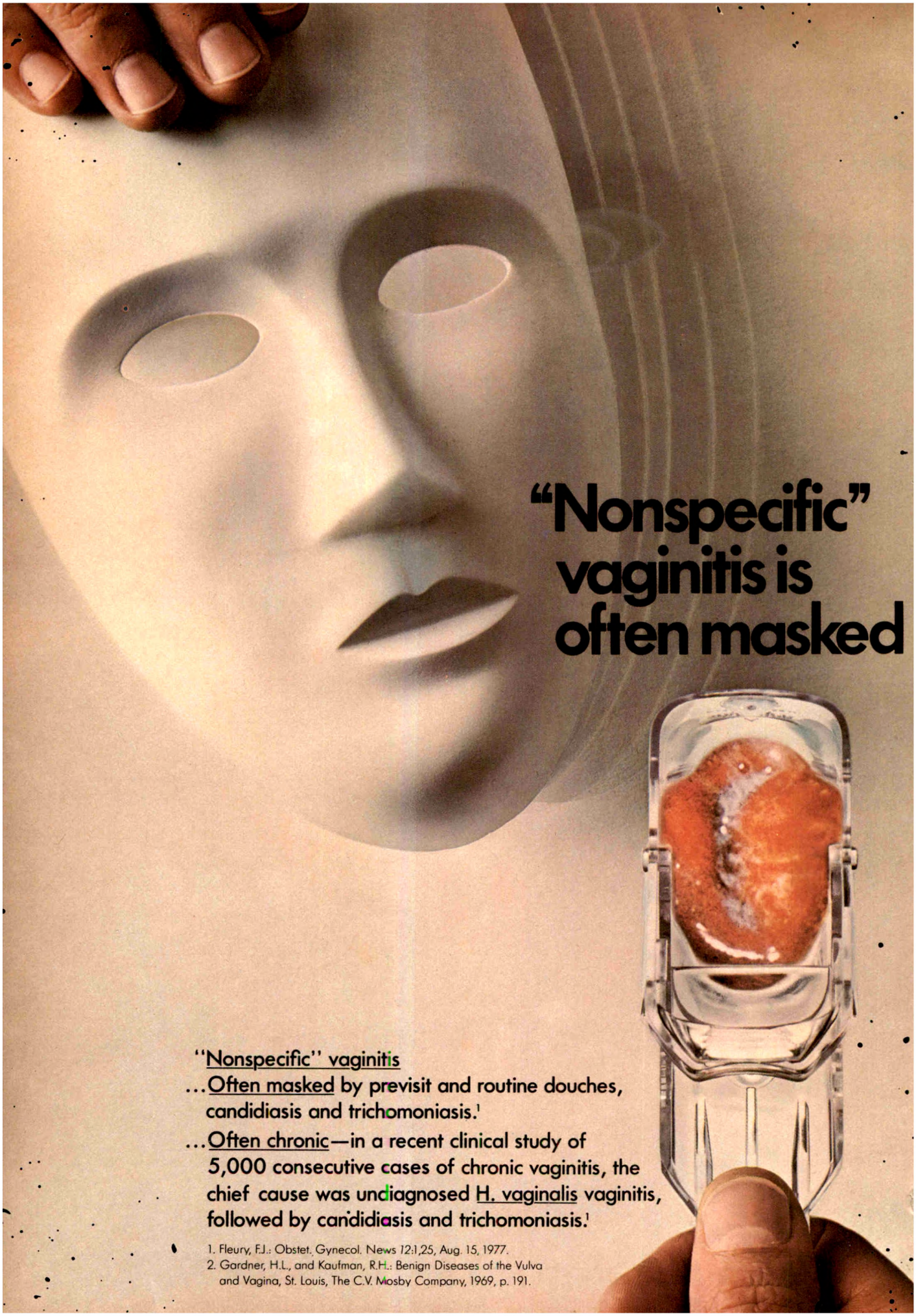
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1. Fleury, F.J.: Obstet. Gynecol. News 12:1,25, Aug. 15, 1977.
2. Gardner, H.L., and Kaufman, R.H.: Benign Diseases of the Vulva and Vagina, St. Louis, The C.V. Mosby Company, 1969, p. 191.

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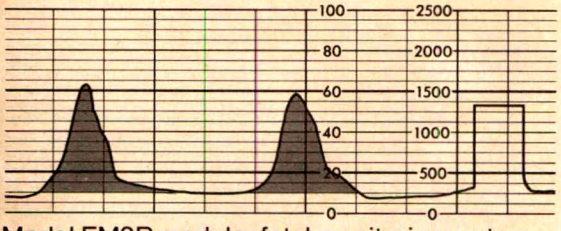
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References: 1. Murad F, Gilman AG: Estrogens and progestins, in Goodman L, Gilman A (eds): The Pharmacological Basis of Therapeutics, ed 5. New York, Macmillan Publishing Co, 1975, p 1423.

2. Klopper A: Treatment of infertility and menopausal symptoms. Br Med J 2:414—416, Aug 1976.

3. Callantine MR, Martin PL, Bolding OT, *et al:* Micronized 17 β-estradiol for oral estrogen therapy in menopausal women. Obstet Gynecol *46*:37, July 1975.

4. Yen SSC, Martin PL, Burnier AM, *et al:* Circulating estradiol, estrone and gonadotropin levels following the administration of orally active 17 β-estradiol in postmenopausal women. J Clin Endocrinol Metab *40*:518, March 1975.

See following page for prescribing information.

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Warning

1. ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA. Three independent case control studies have shown an increased risk of endometrial cancer in postmenopausal women exposed to exogenous estrogens for prolonged periods.[1-3] This risk was independent of the other known risk factors for endometrial cancer. These studies are further supported by the finding that incidence rates of endometrial cancer have increased sharply since 1969 in eight different areas of the United States with population based cancer reporting systems, an increase which may be related to the rapidly expanding use of estrogens during the last decade.[4] The three case control studies reported that the risk of endometrial cancer in estrogen users was about 4.5 to 13.9 times greater than in nonusers. The risk appears to depend on both duration of treatment[1] and on estrogen dose.[3] In view of these findings, when estrogens are used for the treatment of menopausal symptoms, the lowest dose that will control symptoms should be utilized and medication should be discontinued as soon as possible. When prolonged treatment is medically indicated, the patient should be reassessed on at least a semiannual basis to determine the need for continued therapy. Although the evidence must be considered preliminary, one study suggests that cyclic administration of low doses of estrogen may carry less risk than continuous administration;[3] it therefore appears prudent to utilize such a regimen. Close clinical surveillance of all women taking estrogens is important. In all cases of undiagnosed persistent or recurring abnormal vaginal bleeding, adequate diagnostic measures should be undertaken to rule out malignancy. There is no evidence at present that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic doses.

2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY. The use of female sex hormones, both estrogens and progestagens, during early pregnancy may seriously damage the offspring. It has been shown that females exposed *in utero* to diethylstilbestrol, a non-steroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare.[5,6] This risk has been estimated as not greater than 4 per 1000 exposures.[7] Furthermore, a high percentage of such exposed women (from 30 to 90 percent) have been found to have vaginal adenosis,[8-12] epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether they are precursors of malignancy. Although similar data are not available with the use of other estrogens, it cannot be presumed they would not induce similar changes. Several reports suggest an association between intrauterine exposure to female sex hormones and congenital anomalies, including congenital heart defects and limb reduction defects.[13-16] One case control study[16] estimated a 4.7-fold increased risk of limb reduction defects in infants exposed *in utero* to sex hormones (oral contraceptives, hormone withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some of these exposures were very short and involved only a few days of treatment. The data suggest that the risk of limb reduction defects in exposed fetuses is somewhat less than 1 per 1000. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well controlled studies that progestagens are effective for these uses. If Estrace® is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus and the advisability of pregnancy continuation.

Clinical Pharmacology— 17β-Estradiol is the most potent physiologic estrogen and, in fact, is the major estrogenic hormone secreted by the human. Estradiol in Estrace® has been micronized and demonstrated to be rapidly and effectively absorbed from the gastrointestinal tract.[17]

Indications: Estrace® is indicated in the treatment of: 1. Moderate to severe *vasomotor* symptoms associated with the menopause. (There is no evidence that estrogens are effective for nervous symptoms or depression which might occur during menopause, and they should not be used to treat these conditions.) 2. Atrophic vaginitis. 3. Kraurosis vulvae. 4. Female hypogonadism. 5. Female castration. 6. Primary ovarian failure. ESTRACE® HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING).

Contraindications: Estrogens should not be used in women (or men) with any of the following conditions: 1. Known or suspected cancer of the breast except in appropriately selected patients with progressing inoperable or radiation resistant disease. 2. Known or suspected estrogen-dependent neoplasia. 3. Known or suspected pregnancy (See Boxed Warning). 4. Undiagnosed abnormal genital bleeding. 5. Active thrombophlebitis or thromboembolic disorders. 6. A past history of thrombophlebitis or thromboembolic disorders associated with previous estrogen use (except when used in treatment of breast or prostatic malignancy).

Warnings: There is now evidence that estrogens increase the risk of carcinoma of the endometrium in humans. (See Boxed Warning.) At the present time there is no evidence that estrogens given to postmenopausal women increase the risk of cancer of the breast. However, women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms should be administered an estrogen with caution and a careful breast examination should be performed. A recent study has reported a 2 to 3-fold increase in the risk of surgically confirmed gall bladder disease in women receiving postmenopausal estrogens.[18] An increased risk of post-surgery thromboembolic complications has been reported in users of oral contraceptives.[19,20] If feasible, estrogen should be discontinued at least 4 weeks before, and not resumed until at least 4 weeks after, surgery of the type associated with an increased risk of thromboembolism. Estrogens should not be used in persons with thromboembolic disorders and they should not be used (except in treatment of malignancy) in persons with a history of such disorders in association with estrogen use or in patients with cerebral vascular or coronary artery disease. Benign hepatic adenoma should be considered in estrogen users having abdominal pain and tenderness, abdominal mass, or hypovolemic shock. Hepato-cellular carcinoma has also been reported in women taking estrogen-containing oral contraceptives.[21] The relationship of this malignancy to these drugs is not known at this time. There is now evidence that elevated blood pressure occurs with use of estrogens in the menopause[22] and blood pressure should be monitored with estrogen use, especially if high doses are used. Diabetic patients taking estrogens should be carefully observed for decrease in glucose tolerance. Estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases.

Precautions: A complete pretreatment and periodic physical examination should be given to estrogen users with special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolaou smear. Conditions which might be influenced by fluid retention such as epilepsy, migraine, and cardiac or renal dysfunction, require careful observation. Certain patients may develop undesirable manifestations of excessive estrogenic stimulation, such as abnormal or excessive uterine bleeding, mastodynia, etc. Patients with a history of depression should be carefully observed. Preexisting uterine fibromyomata may increase in size while using estrogen. The pathologist should be advised of estrogen therapy when relevant specimens are submitted. If jaundice develops in any patient receiving estrogen, the medication should be discontinued while the cause is investigated. Estrogens should be administered with caution in patients with impaired liver function. Estrogens should be used with caution in patients with metabolic bone diseases that are associated with hypercalcemia or in patients with renal insufficiency. Estrogens should be used judiciously in young patients in whom bone growth is not complete. The following endocrine and liver function tests may be affected with larger doses of estrogen: a. Increased sulfobromophthalein retention; b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability; c. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by PBI, T4 by column, or T4 by radicimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered; d. Impaired glucose tolerance; e. Decreased pregnanediol excretion; f. Reduced response to metyrapone test; g. Reduced serum folate concentration; h. Increased serum triglyceride and phospholipid concentration. As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk.

Adverse Reactions: The following additional adverse reactions have been reported with estrogenic therapy, including oral contraceptives: Breakthrough bleeding, spotting, change in menstrual flow; Dysmenorrhea; Premenstrual-like syndrome; Amenorrhea during and after treatment; Increase in size of uterine fibromyomata; Vaginal candidiasis; Change in cervical eversion and in degree of cervical secretion; Cystitis-like syndrome; Tenderness, enlargement, secretion of the breasts; Nausea, vomiting; Abdominal cramps, bloating; Cholestatic jaundice; Chloasma or melasma which may persist when drug is discontinued; Erythema multiforme; Erythema nodosum; Hemorrhagic eruption; Loss of scalp hair; Hirsutism; Steepening of corneal curvature; Intolerance to contact lenses; Headache, migraine, dizziness; Mental depression; Chorea; Increase or decrease in weight; Reduced carbohydrate tolerance; Aggravation of porphyria; Edema; Changes in libido.

Overdosage: Serious ill effects have not been reported following the ingestion of large doses of estrogen-containing oral contraceptives by young children. Overdosage of estrogen may cause nausea, and withdrawal bleeding may occur in females.

Dosage and Administration: 1. *Given cyclically for short term use only:* For treatment of moderate to severe *vasomotor* symptoms, atrophic vaginitis, or kraurosis vulvae associated with the menopause. The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible. Administration should be cyclic (e.g., 3 weeks on and 1 week off). Attempts to discontinue or taper medication should be made at 3 to 6 month intervals. The usual initial dosage range is 1 or 2 mg. daily of micronized estradiol adjusted as necessary to control presenting symptoms. The minimal effective dose for maintenanace therapy should be determined by titration.

2. *Given cyclically:* Female hypogonadism; female castration; primary ovarian failure. Treatment is usually initiated with a dose of 1 or 2 mg. daily of micronized estradiol, adjusted as necessary to control presenting symptoms; the minimal effective dose for maintenance therapy should be determined by titration.

Treated patients with an intact uterus should be monitored closely for signs of endometrial cancer and appropriate diagnostic measures should be taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

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How Supplied: Estrace 1 mg; lavender scored tablets, NDC 0087-0755-01, bottles of 100. Estrace 2 mg; turquoise scored tablets, NDC 0087-0756-01, bottles of 100.

Full prescribing information is available in the Estrace physician package insert.

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Indications MONISTAT 7 Vaginal Cream is indicated for the local treatment of vulvovaginal candidiasis (moniliasis). As MONISTAT 7 Vaginal Cream is effective only for candidal vulvovaginitis, the diagnosis should be confirmed by KOH smears and/or cultures. Other pathogens commonly associated with vulvovaginitis *(Trichomonas* and *Haemophilus vaginalis)* should be ruled out by appropriate laboratory methods. MONISTAT 7 is effective in both pregnant and non-pregnant women, as well as in women taking oral contraceptives. (See **Precautions**.)

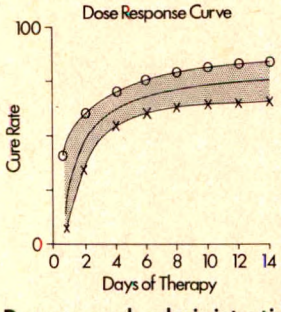
Contraindications Patients known to be hypersensitive to this drug.

Precautions General: Discontinue drug if sensitization or irritation is reported during use. Laboratory Tests: If there is a lack of response to MONISTAT 7, appropriate microbiological studies should be repeated to confirm the diagnosis and rule out other pathogens.

Pregnancy: Since MONISTAT is absorbed in small amounts from the human vagina, it should be used in the first trimester of pregnancy only when the physician considers it essential to the welfare of the patient. Clinical studies, during which MONISTAT was used for 14 days, included 209 pregnant patients. Follow-up reports now available in 117 of these patients reveal no adverse effects or complications attributable to MONISTAT therapy in infants born to these women.

Adverse reactions During clinical studies with MONISTAT for a 14-day regimen, 39 of the 528 patients (7.4%) treated with MONISTAT reported complaints during therapy that were possibly drug-related. Most complaints were reported during the first week of therapy. Vulvovaginal burning, itching or irritation occurred in 6.6%, while other complaints such as vaginal burning, pelvic cramps, hives, skin rash and headache occurred rarely (each less than 0.2% patient incidence). The therapy-related dropout rate was 0.9%.

Clinical Statistical analysis of randomized clinical trials, conducted to determine the shortest effective course of therapy with MONISTAT, demonstrates that a regimen of seven or more days has a cure rate equivalent to the 14-day regimen. The graphic representation of this conclusion plots days of therapy versus cure rates. The solid line represents the mean therapeutic cure rate and the shaded area represents the 95% confidence interval.



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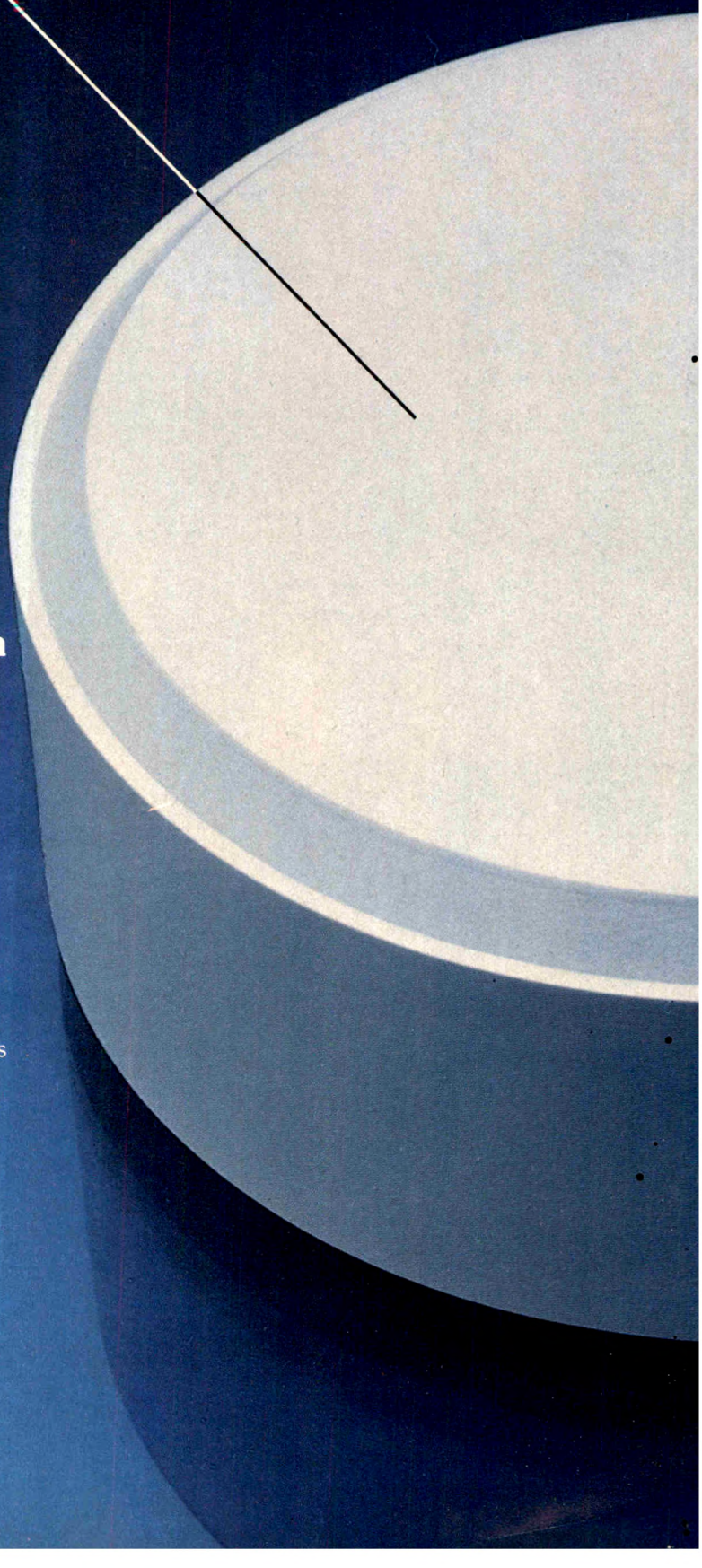
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IN BRIEF:

Indications and Usage—OVRAL® and LO/OVRAL® are indicated for the prevention of pregnancy in women who elect to use oral contraceptives (OC's) as a method of contraception.

Contraindications—OC's should not be used in women with any of the following conditions: 1. Thrombophlebitis or thromboembolic disorders. 2. A past history of deep-vein thrombophlebitis or thromboembolic disorders. 3. Cerebral-vascular or coronary-artery disease. 4. Known or suspected carcinoma of the breast. 5. Known or suspected estrogen-dependent neoplasia. 6. Undiagnosed abnormal genital bleeding. 7. Known or suspected pregnancy (see Warning No. 5).

Warnings

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

The use of oral contraceptives is associated with increased risk of several serious conditions, including thromboembolism, stroke, myocardial infarction, hepatic adenoma, gall bladder disease, hypertension. Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks.

1. *Thromboembolic Disorders and Other Vascular Problems:* An increased risk of thromboembolic and thrombotic disease associated with use of OC's is well-established. Three principal studies in Great Britain and 3 in the U.S. have demonstrated increased risk of fatal and nonfatal venous thromboembolism and stroke, both hemorrhagic and thrombotic. These studies estimate that users of OC's are 4 to 11 times more likely than nonusers to develop these diseases without evident cause.

CEREBROVASCULAR DISORDERS—In a collaborative American study of cerebrovascular disorders in women with and without predisposing causes, it was estimated that the risk of hemorrhagic stroke was 2.0 times greater in users than nonusers and the risk of thrombotic stroke was 4 to 9.5 times greater in users than in nonusers.

MYOCARDIAL INFARCTION (MI)—An increased risk of MI associated with use of OC's has been reported, confirming a previously suspected association. These studies, conducted in the UK, found, as expected, that the greater the number of underlying risk factors for coronary-artery disease (cigarette smoking, hypertension, hypercholesterolemia, obesity, diabetes, history of preeclamptic toxemia) the higher the risk of developing MI, regardless of whether the patient was an OC user or not. OC's, however, were found to be a clear additional risk factor. In terms of relative risk, it has been estimated that OC users who do not smoke (smoking is considered a major predisposing condition to MI) are about twice as likely to have a fatal MI as nonusers who do not smoke. OC users who are also smokers have about a 5-fold increased risk of fatal MI compared to users who do not smoke, but about a 10- to 12-fold increased risk compared to nonusers who do not smoke. Furthermore, amount of smoking is also an important factor. In determining importance of these relative risks, however, baseline rates for various age groups must be given serious consideration. Importance of other predisposing conditions mentioned above in determining relative and absolute risks has not as yet been quantified; quite likely the same synergistic action exists, but perhaps to a lesser extent.

RISK OF DOSE—In an analysis of data derived from several national adverse-reaction reporting systems, British investigators concluded that risk of thromboembolism, including coronary thrombosis, is directly related to dose of estrogen in OC's. Preparations containing 100 mcg or more of estrogen were associated with higher risk of thromboembolism than those containing 50-80 mcg. Their analysis did suggest, however, that quantity of estrogen may not be the sole factor involved. This finding has been confirmed in the U.S.

ESTIMATE OF EXCESS MORTALITY FROM CIRCULATORY DISEASES—A large prospective study carried out in the UK estimated the mortality rate per 100,000 women per year from diseases of the circulatory system for users and nonusers of OC's according to age, smoking habits, and duration of use. Overall excess death rate annually from circulatory diseases for OC users was estimated to be 20 per 100,000 (ages 15-34—5/100,000; ages 35-44—33/100,000; ages 45-49—140/100,000), risk being concentrated in older women, in those with long duration of use, and in cigarette smokers. It was not possible, however, to examine interrelationships of age, smoking, and duration of use, nor to compare effects of continuous vs. intermittent use. Although the study showed a 10-fold increase in death due to circulatory diseases in users for 5 or more years, all these deaths occurred in women 35 or older. Until larger numbers of women under 35 with continuous use for 5 or more years are available, it is not possible to assess magnitude of relative risk for this younger group.

Available data from a variety of sources have been analyzed to estimate risk of death associated with various methods of contraception. Estimates of risk of death for each method include combined risk of contraceptive method (e.g. thromboembolic and thrombotic disease in the case of OC's) plus risk attributable to pregnancy or abortion in event of method failure. This latter risk varies with effectiveness of method. The study concluded that mortality associated with all methods of birth control is low and below that associated with childbirth, with the exception of OC's in women over 40 who smoke. Lowest mortality is associated with condom or diaphragm backed up by early abortion. Risk of thromboembolic and thrombotic disease associated with OC's increases with age after about 30 and, for MI, is further increased by hypertension, hypercholesterolemia, obesity, diabetes, or history of preeclamptic toxemia, and especially cigarette smoking.

Physician and patient should be alert to earliest manifestations of thromboembolic and thrombotic disorders (e.g., thrombophlebitis, pulmonary embolism, cerebrovascular insufficiency, coronary occlusion, retinal thrombosis, and mesenteric thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately. A 4- to 6-fold increased risk of postsurgery thromboembolic complications has been reported in OC users. If feasible, OC's should be discontinued at least 4 weeks before surgery of a type associated with increased risk of thromboembolism or prolonged immobilization.

2. *Ocular Lesions*—There have been reports of neuro-ocular lesions such as optic neuritis or retinal thrombosis associated with use of OC's. Discontinue OC's if there is unexplained, sudden or gradual, partial or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal-vascular lesions, and institute appropriate diagnostic and therapeutic measures.

3. *Carcinoma*—Long-term continuous administration of either natural or synthetic estrogen in certain animal species increases frequency of carcinoma of the breast, cervix, vagina, and liver. Certain synthetic progestogens, none currently contained in OC's, have been noted to increase incidence of mammary nodules, benign and malignant, in dogs. In humans, 3 case-control studies have reported an increased risk of endometrial carcinoma associated with prolonged use of exogenous estrogen in postmenopausal women. One publication reported on the first 21 cases submitted by physicians to a registry of cases of adenocarcinoma of the endometrium in women under 40 on OC's. Of cases found in women without predisposing risk factors (e.g., irregular bleeding at the time OC's were first given, polycystic ovaries), nearly all occurred in women who had used a sequential OC. These are no longer marketed. No evidence has been reported suggesting increased risk of endometrial cancer in users of conventional combination or progestogen-only OC's. Several studies have found no increase in breast cancer in women taking OC's or estrogens. One study, however, while also noting no overall increased risk of breast cancer in women on OC's, found an excess risk in subgroups of OC users with documented benign breast disease. Reduced occurrence of benign breast tumors in users of OC's has been well-documented. In summary, there is at present no confirmed evidence from human studies of increased risk of cancer associated with OC's. Close clinical surveillance of all women on OC's is, nevertheless, essential. In all cases of undiagnosed persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be taken to rule out malignancy. Women with a strong family history of breast cancer or with breast nodules, fibrocystic disease, or abnormal mammograms should be monitored with particular care if they elect to use OC's.

4. *Hepatic Tumors*—Benign hepatic adenomas have been found to be associated with use of OC's. One study showed that OC's with high hormonal potency were associated with higher risk than lower potency OC's. Although benign, hepatic adenomas may rupture and may cause death through intra-abdominal hemorrhage. This has been reported in short-term as well as long-term users. Two studies relate risk with duration of use of OC's, the risk being much greater after 4 or more years' use. While hepatic adenoma is rare, it should be considered in women presenting abdominal pain and tenderness, abdominal mass or shock. A few cases of hepatocellular carcinoma have been reported in women on OC's. Relationship of these drugs to this type of malignancy is not known.

5. *Use in or Immediately Preceding Pregnancy, Birth Defects in Offspring, and Malignancy in Female Offspring*—Use of female sex hormones—both estrogenic and progestational agents—during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a nonsteroidal estrogen, have increased risk of developing in later life a form of vaginal or cervical cancer ordinarily extremely rare. This risk has been estimated to be of the order of 1 in 1,000 exposures or less. Although there is no evidence now that OC's further enhance risk of developing this type of malignancy, such patients should be monitored with particular care if they elect to use OC's. Furthermore, 30 to 90% of such exposed women have been found to have epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether this condition is a precursor of vaginal malignancy. Male children so exposed may develop abnormalities of the urogenital tract.

Although similar data are not available with use of other estrogens, it cannot be presumed they would not induce similar changes. An increased risk of congenital anomalies, including heart defects and limb defects, has been reported with use of sex hormones, including OC's, in pregnancy. One case-control study estimated a 4.7-fold increase in risk of limb-reduction defects in infants exposed in utero to sex hormones (OC's, hormonal withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some exposures involved only a few days. Data suggest that risk of limb-reduction defects in exposed fetuses is somewhat less than 1 in 1,000 live births. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well-controlled studies that progestogens are effective. There is some evidence that triploidy and possibly other types of polyploidy are increased among abortuses from women who become pregnant soon after ceasing OC's. Embryos with these anomalies are virtually always aborted spontaneously. Whether there is an overall increase in spontaneous abortion of pregnancies conceived soon after stopping OC's is unknown. It is recommended that, for any patient who has missed 2 consecutive periods, pregnancy should be ruled out before continuing OC's. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at time of first missed period, and further use of OC's should be withheld until pregnancy has been ruled out. If pregnancy is confirmed, the patient should be apprised of the potential risks to the fetus, and advisability of continuation of the pregnancy should be discussed. It is also recommended that women who discontinue OC's with intent of becoming pregnant use an alternate form of contraception for a period of time before attempting to conceive. Many clinicians recommend 3 months, although no precise information is available on which to base this. The administration of progestogen-estrogen combinations to induce withdrawal bleeding should not be used as a test of pregnancy.

6. *Gallbladder Disease*—Studies report increased risk of surgically confirmed gallbladder disease in users of OC's and estrogens. In one study, increased risk appeared after 2 years' use and doubled after 4 or 5 years' use. In one of the other studies, increased risk was apparent between 6 and 12 months' use.

7. *Carbohydrate and Lipid Metabolic Effects*—Decrease in glucose tolerance has been observed in a significant percentage of patients on OC's. For this reason, prediabetic and diabetic patients should be carefully observed while on OC's. Increase in triglycerides and total phospholipids has been observed in patients on OC's; clinical significance of this finding remains to be defined.

8. *Elevated Blood Pressure*—Increase in blood pressure has been reported in patients on OC's. In some women, hypertension may occur within a few months of beginning OC's. In the 1st year of use, prevalence of women with hypertension is low in users and may be no higher than that of a comparable group of nonusers. Prevalence in users increases, however, with longer exposure, and in the 5th year of use is 2½ to 3 times the reported prevalence in the 1st year. Age is also strongly correlated with development of hypertension in OC users. Women who previously have had hypertension during pregnancy may be more likely to develop elevation of blood pressure on OC's. Hypertension that develops as a result of taking OC's usually returns to normal after discontinuing the drug.

9. *Headache*—Onset or exacerbation of migraine or development of headache of a new pattern which is recurrent, persistent, or severe, requires discontinuation of OC's and evaluation of the cause.

10. *Bleeding Irregularities*—Breakthrough bleeding, spotting, and amenorrhea are frequent reasons for patients discontinuing OC's. In breakthrough bleeding, as in all cases of irregular vaginal bleeding, nonfunctional causes should be borne in mind. In undiagnosed persistent or recurrent abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy. If pathology has been excluded, time or change to another OC may solve the problem. Changing to an OC with a higher estrogen content, while potentially useful in minimizing menstrual irregularity, should be done only if necessary, since this may increase risk of thromboembolic disease.

Women with past history of oligomenorrhea or secondary amenorrhea or young women without regular cycles may have a tendency to remain anovulatory or to become amenorrheic after discontinuing OC's. Women with these preexisting problems should be advised of this possibility and encouraged to use other methods. Post-use anovulation, possibly prolonged, may also occur in women without previous irregularities.

11. *Ectopic Pregnancy*—Ectopic as well as intrauterine pregnancy may occur in contraceptive failures.

12. *Breast-feeding*—OC's given in the postpartum period may interfere with lactation and decrease quantity and quality of breast milk. Furthermore, a small fraction of the hormones in OC's has been identified in the milk of mothers on OC's; effects, if any, on the breast-fed child have not been determined. If feasible, defer OC's until infant has been weaned.

Precautions—GENERAL—1. A complete medical and family history should be taken prior to initiation of OC's. Pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen and pelvic organs, including Pap smear and relevant laboratory tests. As a general rule OC's should not be prescribed for longer than 1 year without another physical examination.

2. Under influence of estrogen-progestogen preparations, pre-existing uterine leiomyomata may increase in size.

3. Patients with history of psychic depression should be carefully observed and the drug discontinued if depression recurs to a serious degree. Patients becoming significantly depressed while on OC's should stop OC's and use an alternate method to try to determine whether the symptom is drug-related.

4. OC's may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention, such as convulsive disorders, migraine syndrome, asthma, or cardiac or renal insufficiency.

5. Patients with a past history of jaundice during pregnancy have an increased risk of recurrence while on OC's. If jaundice develops, OC's should be discontinued.

6. Steroid hormones may be poorly metabolized in patients with impaired liver function and should be administered with caution.

7. OC users may have disturbances in normal tryptophan metabolism which may result in a relative pyridoxine deficiency. Clinical significance is undetermined.

8. Serum folate levels may be depressed by OC's. Since the pregnant woman is predisposed to development of folate deficiency and incidence of folate deficiency increases with increasing gestation, it is possible that if a woman becomes pregnant shortly after stopping OC's, she may have a greater chance of developing folate deficiency and complications attributed to this deficiency.

9. The pathologist should be advised of OC therapy when relevant specimens are submitted.

10. Certain endocrine- and liver-function tests and blood components may be affected by estrogen-containing OC's: a. Increased sulfobromophthalein retention. b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability. c. Increased thyroid-binding globulin (TBG) leading to increased circulating total-thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered. d. Decreased pregnanediol excretion. e. Reduced response to metyrapone test.

Information for the Patient—See Patient Package Labeling.

Drug Interactions—Reduced efficacy and increased incidence of breakthrough bleeding have been associated with concomitant use of rifampin. A similar association has been suggested with barbiturates, phenylbutazone, phenytoin sodium, and ampicillin.

Carcinogenesis—See Warnings on carcinogenic potential of OC's.

Pregnancy—Category X. See Contraindications, Warnings.

Nursing Mothers—See Warnings.

Adverse Reactions—An increased risk of these serious adverse reactions has been associated with use of OC's (see Warnings): thrombophlebitis, pulmonary embolism, coronary thrombosis, cerebral thrombosis, cerebral hemorrhage, hypertension, gallbladder disease, benign hepatomas, congenital anomalies. There is evidence of an association between the following conditions and use of OC's although additional confirmatory studies are needed: mesenteric thrombosis, neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis.

The following adverse reactions have been reported in patients on OC's and are believed to be drug-related. Nausea and/or vomiting, usually the most common adverse reactions, occur in approximately 10 percent or less of patients during the first cycle. Other reactions, as a general rule, are seen much less frequently or only occasionally. Gastrointestinal symptoms (such as abdominal cramps and bloating); breakthrough bleeding, spotting, change in menstrual flow; dysmenorrhea, amenorrhea during and after treatment, temporary infertility after discontinuance of treatment; edema; chloasma or melasma which may persist; breast changes: tenderness, enlargement, and secretion; change in weight (increase or decrease); change in cervical erosion and cervical secretion; possible diminution in lactation when given immediately postpartum; cholestatic jaundice; migraine; increase in size of uterine leiomyomata; rash (allergic); mental depression; reduced tolerance to carbohydrates; vaginal candidiasis; change in corneal curvature (steepening), intolerance to contact lenses.

The following adverse reactions have been reported in users of OC's, and the association has been neither confirmed nor refuted: premenstrual-like syndrome, cataracts, changes in libido, chorea, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption, vaginitis, porphyria.

Acute Overdose—Serious ill effects have not been reported following acute ingestion of large doses of OC's by young children. Overdosage may cause nausea, and withdrawal bleeding may occur in females.

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OBSTETRICS

Elevated plasma prolactin concentration in cholestasis of pregnancy

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The plasma concentrations of prolactin and estradiol-17β were measured by specific radioimmunoassays in 150 women with normal pregnancies and 76 women with cholestasis of pregnancy. At 33 to 34 weeks of gestation plasma prolactin concentrations were 187 ± 23 ng/ml (mean ± S.E.M.) for normal pregnancy and 341 ± 38 ng/ml for cholestasis ($p < 0.001$). At 35 to 36 weeks they were 254 ± 24 and 355 ± 26 ng/ml ($p < 0.01$), and at 37 to 38 weeks 175 ± 14 and 365 ± 34 ng/ml ($p < 0.001$), respectively. Higher prolactin levels in the cholestasis group were not related to differences in plasma estradiol-17β concentrations. No correlation was found between plasma prolactin and serum aminotransferase levels, or between prolactin levels and placental weight. The mechanisms by which plasma prolactin levels become elevated in cholestasis of pregnancy remain to be elucidated. (AM. J. OBSTET. GYNECOL. 134:1, 1979.)

PLASMA PROLACTIN levels increase progressively during pregnancy.[1–3] This has been ascribed to stimulation of maternal pituitary galactotrophs by placental estrogens. In early pregnancy the prolactin concentration of amniotic fluid considerably exceeds that of maternal or fetal serum.[4, 5] and it has been suggested that the placenta contributes to this elevation.[6, 7]

Only a few reports describe maternal plasma prolactin levels in pathologic states of pregnancy. Elevated concentrations have been claimed to occur in pregnancies with severe pre-eclamptic toxemia,[8] but this has not been found in all studies.[9]

Cholestasis complicates about 1% of all pregnancies in Finland and Scandinavia, and it is characterized by elevated serum aminotransferase levels, itching, and sometimes jaundice.[10] The placenta shows characteristic features of edema in the chorion villi, but otherwise no characteristic changes have been observed in the fetoplacental unit. Cholestasis is associated with an increased frequency of near-term intrauterine fetal

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Table I. Mean plasma prolactin concentrations (ng/ml) ± S.E.M. in normal pregnancies and in cholestasis of pregnancy

Weeks of pregnancy	*N*	*Normal pregnancy*	*N*	*Cholestasis*
33-34	30	187 ± 23	54	341 ± 38*.
35-36	37	254 ± 24	70	355 ± 26†
37-38	56	175 ± 14	45	365 ± 34*

*$p < 0.001$.
†$p < 0.01$.

Table II. Mean plasma estradiol-17β concentrations (ng/ml) ± S.E.M. in normal pregnancy and in cholestasis of pregnancy

Weeks of pregnancy	*N*	*Normal pregnancy*	*N*	*Cholestasis*
33-34	49	21.5 ± 1.2	56	20.6 ± 1.5*
35-36	40	24.8 ± 2.2	76	26.7 ± 1.7*
37-38	61	26.3 ± 1.4	49	25.8 ± 1.8*

*P value not significant.

deaths for so far unknown reasons, and attempts at demonstrating impending intrauterine death by biochemical markers have proved unrewarding.[11] In search of biochemical changes in cholestasis of pregnancy we studied the plasma prolactin levels in this pregnancy complication.

Patients and methods

Plasma samples were collected from 150 women with normal pregnancies between 33 and 38 weeks at the Departments I and II of Obstetrics and Gynecology, University Central Hospital, Helsinki. All women were delivered of healthy infants at term. Specimens from these pregnancies served as controls for normal plasma prolactin and estradiol concentrations in late pregnancy. Cholestasis was diagnosed in 76 women. All had elevated serum aminotransferase levels over 50 U/L.[12] Altogether 181 plasma samples from 33 to 38 weeks of gestation were collected from these pregnancies. Plasma samples were stored at −20° C until assayed.

Plasma prolactin levels were measured by a homologous radioimmunoassay (prolactin standard V.L.S.3, National Institute of Arthritis, Metabolism, and Digestive Diseases, Bethesda, Maryland) as described.[13] All samples were measured in the same assay with a 10% intra-assay coefficient of variation at concentrations between 150 and 250 ng/ml. Reportedly human placental lactogen (hPL) does not cross-react with the prolactin assay we used,[14] and we found a 0.1% cross reaction with purified hPL.

Plasma estradiol levels were measured by radioimmunoassay using 2,4,6,7,-^{3}H-estradiol (NET-317, S.A. 110 Ci/mmol, New England Nuclear, Boston, Massachusetts, and antiserum donated by Dr. B. S. Lindberg, Uppsala, Sweden). The specificity of antiserum has been described.[15, 16] The interassay coefficient of variation of 13 assays was 14% at a final concentration of 25 ng/ml.

Student's t test was used for statistical analysis of differences between normal and cholestasis groups. Correlations between individual prolactin and aminotransferase levels, and between prolactin and placental weight, were studied by Spearman correlation analysis.

Results

In normal pregnancy the mean plasma prolactin levels were from 175 to 254 ng/ml in the third trimester. In cholestatic pregnancy the plasma prolactin concentrations were significantly higher than normal at all stages of gestation. The mean levels were from 341 to 365 ng/ml in the third trimester (Table I).

The concentrations of plasma estradiol were similar in normal and cholestatic pregnancy (Table II). Plasma prolactin concentrations were not correlated with serum aminotransferase levels ($R = -0.023$) or with placental weight ($R = 0.185$).

Comment

Our results show that in cholestasis of pregnancy the plasma prolactin concentrations are significantly higher than in normal pregnancy. This does not seem to be related to circulating plasma estrogen levels or to the severity of maternal disease as based on serum aminotransferase levels. Moreover, no correlation was found between the placental weight and maternal plasma prolactin concentrations.

Elevated prolactin levels in cholestasis may be due to decreased elimination or increased synthesis of prolactin. Decreased metabolism of prolactin has neither been confirmed nor excluded. During gestation prolactin is secreted from fetal and maternal pituitary.[1, 2, 7] We are not able to say whether increased pituitary prolactin secretion is responsible for the difference we observed, but disturbance in the neurotransmitter control of pituitary hormone secretion has been suggested to occur in chronic hepatic failure.[17]

Placental synthesis of prolactin has been proposed,[8] and increased placental production of prolactin must be considered, as one possibility. Human placental lactogen has also been found at elevated concentrations in cholestasis of pregnancy.[11] The 0.1% cross reaction with hPL in the prolactin assay was not responsible for the far higher prolactin level seen in these patients.

Further work is now underway to uncover the mechanisms leading to elevated maternal plasma prolactin concentrations in cholestasis of pregnancy, and to find out whether they bear any relationship to the fetal outcome. However, we have seen no intrauterine fetal deaths since we adopted a practice of inducing labor before the onset of the thirty-ninth pregnancy week.

We are grateful to the National Pituitary Agency, National Institute of Arthritis, Metabolism, and Digestive Diseases, Bethesda, Maryland for supplying us with purified prolactin and the antisera, to Dr. B. S. Lindberg, Uppsala, Sweden, for antiestradiol-17β antiserum, and to Ms. Liisa Airas, Ms. Seija Nikunen, and Ms. Anne Mäkelä for technical assistance.

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Screening for alcohol-related problems in an outpatient obstetric-gynecologic clinic

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Three methods of screening for alcohol-related problems were tested in 499 of 565 consecutive patients in an obstetric-gynecologic outpatient clinic. The methods included a 31 item self-administered questionnaire, a six-item physician-administered questionnaire, and a blood alcohol test. Medical records were reviewed for mention of conditions sometimes associated with alcohol use. Sixteen percent of the women were heavy drinkers, and 18% were found on screening to be probable or potential problem drinkers. In women under age 40 years heavy drinking was associated with a higher incidence of physical problems sometimes associated with excessive alcohol use, and significantly lower birth weights were observed in infants born to obstetric patients who were positive on screening for alcohol-related problems. (AM. J. OBSTET. GYNECOL. 134:4, 1979.)

THE PRESENT STUDY is the first phase of a program to explore the feasibility of screening obstetric and gynecologic patients for alcohol- and other drug–related problems. This program was initiated in response to data which indicate that these patients may be at high risk for alcohol-related problems. Studies of alcoholic women reveal an excess of obstetric and gynecologic problems, such as repeated spontaneous abortion,[1] postpartum depression,[2, 3] infertility,[1, 4, 5] and hysterectomy.[5] Both cause and effect have been invoked to account for the association. Alcoholism and heavy drinking are linked to a stressful, precipitating factor more often in female than in male subjects,[1–3] and obstetric-gynecologic problems are among those often cited by women as the cause of their chronic, excessive use of alcohol. At the same time, there is evidence that alcohol is a gonadal toxin,[6] and heavy drinking may contribute to obstetric-gynecologic problems in some women. In addition to the potentially harmful effect of alcohol use on women themselves, it has been recently reported that the excessive use of alcohol during pregnancy is associated with the fetal alcohol syndrome, characterized by retarded intrauterine growth, mental retardation, and a distinctive pattern of congenital anomalies.[7]

These are the factors that motivated the present study in which several methods to screen for alcohol-related problems were tested in an obstetric-gynecologic outpatient clinic. This study addresses some of the following questions: Would obstetric-gynecologic patients cooperate in a study of problems related to their use of alcohol? Would they answer honestly? How sensitive and specific are the screening measures tested? Is there any evidence to support the suggestion that obstetric-gynecologic patients are at high risk for alcohol-related problems? Is the use of alcohol significantly related to health problems of patients and their offspring? Do the test results provide support for the incorporation of screening for alcohol-related problems as part of the routine care of the clinic patients?

Methods

The sample consisted of 565 women seen consecutively during the summer of 1975 in the obstetric-gynecologic outpatient clinic of a general hospital in the inner city of Buffalo. Eighty-eight percent of the sample agreed to participate in the study, for a final sample of 499 women. Reasons for refusals included the following, with about 1% to 2% of the population in each group: minors for whom parental consent was not obtained, mentally retarded individuals, people who were too sick, elderly people who were confused or

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suspicious, women who thought their husbands would object, and some who were against surveys in general. In fewer than 1% of the cases was there reason to suspect an alcohol problem was related to refusal to cooperate. Women were mainly lower and lower-middle class; approximately 35% were Caucasian and 65% black; 88 were pregnant, and 411 were gynecologic patients.

The screening methods tested are described below.

A self-administered questionnaire. This was completed in about 10 to 15 minutes while the women waited to see their doctors; it consisted of 31 questions: eight on sociodemographic characteristics, one on smoking, 12 on alcohol use, and 10 on alcohol-related problems. Women were considered positive on screening if they reported heavy alcohol use and/or two or more alcohol-related problems.

Heavy alcohol use. Women were asked how often they drank wine, beer, and liquor, and how often they had five or more drinks, three or four drinks, and one or two drinks of each beverage. These questions on the use of alcohol were used to identify heavy drinkers according to three of the most widely used drinking pattern classification schemes.

THE QUANTITY-FREQUENCY-VARIABILITY INDEX (QFV). Heavy drinking ranges from people who drink three times or more daily regardless of quantity to those who drink two to three times a month but who have five or more drinks more than half the time.[8]

THE ABSOLUTE ALCOHOL INDEX (AA). One or more ounces of absolute alcohol per average day is considered heavy drinking. This corresponds to an average daily intake of two cocktails *or* two glasses of wine *or* two and a half cans of beer or *more*.[9]

THE VOLUME-VARIABILITY INDEX (VV). Heavy drinking is defined as an average daily intake of 1.5 drinks or more and five or more drinks at a time at least once in a while.[8]

Alcohol-related problems. The Self-Administered Alcohol Screening Test of Swenson and Morse[10] was adapted for use in a female population by eliminating questions about behavior that is more typical of male than female alcohol abuse, such as having fist fights after drinking. Also eliminated were questions such as those about attendance at Alcoholics Anonymous meetings which might have intimidated some of the patients and which tend to identify individuals whose problems with alcohol had already been recognized and addressed.

The Cage screening test.[11] This is a series of six alcohol-related questions asked by the physician during his examination: two introductory questions and four test questions on alcohol-related problems. Patients who reported two or more problems were considered positive on screening.

Table I. Heavy drinkers among obstetric and gynecologic clinic patients as measured by three classification systems

Drinking classifications defining heavy drinkers	*Obstetric (N = 88)*	*Gynecologic (N = 411)*	*Total (N = 499)*
QFV	8% (7)	15% (61)	14% (68)
AA (ounces per average day)	6% (5)	11% (46)	10% (51)
VV	6% (5)	12% (50)	11% (55)
QFV or AA or VV	9% (8)	17% (71)	16% (79)
QFV and AA and VV	5% (4)	10% (40)	9% (44)

Blood alcohol test. Blood alcohol concentrations were analyzed only for women who were having blood drawn for other purposes; determinations were made for 12% of the study population (62 of 499). Casual blood alcohol levels over 100 mg/100 ml are considered positive screening results.

Medical record review. Patients' records were reviewed for mention of excess use of alcohol or problems related to alcohol, diseases or mental conditions possibly related to the use of alcohol, and results of laboratory tests associated with excess alcohol use (see Appendices). Mention of alcohol-related problems in the chart was considered to be evidence that clinic personnel were aware of a probable or potential drinking problem.

Summary screening score.* In addition to evaluating patients in terms of their scores on individual screening tests, data from all the available sources, the self-administered screening test, the Cage questions, the blood tests, and the medical record review were pooled for an overall summary screening score. The rationale for summarizing the data in this fashion derives from consideration of the recommendations of the National Council on Alcoholism Criteria Committee for the Diagnosis of Alcoholism.[12] The Committee cites disorders such as liver disease, chronic gastritis, peripheral neuropathy, or anemia in a person who drinks regularly as probably indicative of problem drinking, and it further states that laboratory tests associated with these conditions, such as elevated serum glutamic oxalacetic transaminase levels and abnormal blood tests, may arouse suspicion of an alcohol problem. As well as dis-

*Details on construction of the summary screening score are available from the first author.

Table II. Drinking patterns* observed in the clinic population compared to those expected, Caucasians only†

Drinking classification	*Obstetric*		*Gynecologic*		*Total*	
	Observed	*Expected*	*Observed*	*Expected*	*Observed*	*Expected*
Heavy	3	4.8	18	19.2	21	24.0
Moderate	4	7.0	23	33.5	26	40.5
Light	4	5.6	18	41.9	23	47.5
Infrequent	6	3.7	28	24.5	34	28.2
Abstainers	6	1.9	48	15.9	54	17.8
Total	23	23.0	135	135.0	158	158.0
Significance	P = 0.05‡		P = 0.0001		P = 0.0001	

*According to the QFV Index of Cahalan and associates, 1969.[8]

†Expected drinking patterns based on age- and race-specific rates of drinking in a probability sample of the adult female household population.[14] Reliable data on drinking patterns among blacks are not available.

‡Because of small numbers, heavy, moderate, and light drinkers were grouped as were infrequent drinkers and abstainers in testing the significance of the difference between the observed and expected distributions for obstetric patients.

Table III. Percent of obstetric-gynecologic clinic patients reporting alcohol-related behavior, by age

Alcohol-related behavior	*Age*			*Total (N = 499)*
	14 to 29 yr. (N = 320)*	*30 to 39 yr. (N = 65)*	*40 to 76 yr. (N = 114)*	
Heavy drinking (QFV or AA or VV)	18%	23%	6%	16%
Two or more problems†	13%	25%	12%	14%
One or more physical conditions‡	32%	49%	72%	46%
One or more mental conditions‡	11%	29%	40%	19%
Reference in medical record	1%	13%	12%	5%

*Thirteen of the patients were less than age 18 years, the legal age for buying alcoholic beverages in New York State.

†Reported on self-administered questionnaire or physician-administered Cage instrument.

‡Conditions sometimes associated with the excessive use of alcohol (see Appendices).

cussing physiologic and clinical criteria for the diagnosis of alcoholism (Track 1), the National Council on Alcoholism Criteria Committee has identified behavioral, psychological, and attitudinal criteria (Track 2), such as being criticized by one's spouse, which may indicate problem drinking, and it has recommended that criteria from both tracks be sought in making a diagnosis. The self-administered questionnaire and Cage questions provide data on alcohol-related behavioral criteria, and the medical record and laboratory tests provide data on physiologic and clinical criteria; therefore, these data were combined in final evaluation of the patients. Women who were found to have either physiologic/clinical or psychological/attitudinal factors associated with heavy alcohol use were designated probable problem drinkers on the summary screening score.

Analysis of screening results and consultation notes for women who were diagnosed as problem drinkers by the counselors but who were missed by the screening procedures revealed that most were young women (average age 26 years, ±12 [SD]) who were heavy drinkers (average AA 2.5 ounces ± 1.8 [SD]). They had not yet developed physical problems related to their heavy use of alcohol; they had no work or study ambitions to interfere with their drinking; and they associated with people who were not critical of their drinking patterns. Inasmuch as continued heavy use of alcohol seems likely to lead to problems in the future, patients who consumed more than one ounce of absolute alcohol per average day were designated potential problem drinkers on the summary screening score.

In order to validate the screening tests, every tenth patient was asked to stay for a diagnostic consultation with an experienced alcoholism counselor or consultant. The alcoholism counselors were not always available and in some cases patients could not or would not stay to talk with them; therefore, in the latter phase of the

Table IV. Report of alcohol-related behaviors as they relate to positive summary screening scores in an obstetric-gynecologic clinic population

Alcohol-related behavior	*Individuals reporting behavior (%)*	*Individuals positive on screening who reported behavior (%)*	*Individuals reporting behavior who are positive on screening (%)*
Self-administered questionnaire (N = 499):			
Ever had a blackout	15	55*	65
Friends/relatives worried in past year about her drinking	5	25*	85
Cannot stop drinking at will	4	13*	65
Drinking sometimes leads to problems with family	6	28*	77
Drinks sometimes in the morning	3	16*	93
Feels need sometimes to cut down on drinking	15	48*	59
Has *ever* sought help for drinking	3	12*	67
Relatives/friends *ever* sought help for her drinking	2	8*	64
Ever told by doctor to stop drinking	5	21	78
Sought help for an emotional problem (ever)	20	33	30
Parents have drinking problem	26	42*	28
Sibs have drinking problem	16	23	25
Husband has drinking problem	14	18	23
Children have drinking problem	3	2	15
Physician-administered "Cage" questions (N = 310):			
Ever felt she should *cut* down	7	29*	81*
Ever *annoyed* by criticism of her drinking	4	16*	82
Ever felt bad or *guilty* about her drinking	5	22*	81
Ever drink in the morning *(eye opener)*	1	7*	100
Heavy drinking reported on self-administered questionnaire (N = 499):			
QFV or AA or VV	16	72*	65
QFV and AA and VV	9	50*	100†
References to alcohol-related problems in the medical record	5	25*	85

*P < 0.001.
†By definition.

study every fifth patient was asked to stay for a consultation.

In addition to interviewing randomly selected patients, counselors also saw patients for whom the examining physicians requested a consultation, and attempts were made to follow up patients with positive scores on the screening test. In order to avoid possible bias in the counselors' evaluations, it was also planned to schedule follow-up consultations with subjects who had negative findings on the screening tests who were similar to the screen-positive patients in age, race, marital status, and educational background. Difficulties in locating patients for follow-up interviews, plus the unexpected resignation of the key counselor in the program, reduced the number of follow-up interviews that could be completed. Given this limitation, it was necessary to concentrate on the patients who were positive on screening in order to determine whether they would be considered by alcoholism treatment personnel to have alcohol-related problems serious enough to warrant referral. This decision was motivated by concern for the health of patients who scored positively on screening, as well as by the need to validate the screening instruments.

Table V. Comparison of responses to similar questions on self-administered and physician-administered cage screening tests (N = 310)

Question	*Cage: Physician-administered*		
	Yes	*No*	*Total*
Self-administered:			
Feels/ever felt need to cut down on drinking			
Yes	12	33	45
No	9	256	265
Total	21	289	310
Drinks sometimes/ever drinks in the morning			
Yes	2	7	9
No	2	298	300
Total	4	305	309

Despite this departure from the original study design, the potential for bias is limited by the fact that counselors had a list of symptoms to be checked with each patient which provided a framework for consistency in the consultations. Final diagnoses were based on review of the consultative notes by the authors with-

Table VI. Patient classification according to summary screening score and alcoholism counsellors' diagnostic consultation

Summary screening score	*Diagnostic consultation*			*No diagnostic consultation*	*Total*
	Problem drinkers	*Potential problem drinkers*	*No significant alcohol problems*		
Probable problem drinkers	14	0	2	45	61 (12.2%)
Potential problem drinkers	5	10	2	10	27 (5.4%)
No significant alcohol problems	0	3	32	376	411 (82.4%)
Total	19	13	36	431	499 (100%)

out regard to whether a patient had been selected randomly or on the basis of positive screening results. All in all, diagnostic consultations were obtained in 68 cases. Patients who were found to have significant problems related to their alcohol use were given counseling and referred to appropriate community mental health care programs for additional help as needed.

The records of obstetric patients in the screening program were re-reviewed after screening to determine the outcome of their pregnancies. Delivery and birth records were reviewed for those who were delivered, and information was abstracted on complications associated with labor and on the condition of the baby at birth.

Results

The proportions of obstetric and gynecologic patients identified as heavy drinkers according to the three classification systems, singly and in combination, are compared in Table I. Approximately half as many obstetric patients as gynecologic patients drink heavily, regardless of the index used. Overall estimates of heavy drinking in the clinic population range between 10% and 14%. The failure of any one index to identify all heavy drinkers is indicated by the fact that the proportion of patients identified by any one index (16%) and the proportion defined by all three indices (9%) lie outside the range identified by any of the three indices singly.

In Table II the distribution of the drinking patterns among clinic patients, indirectly adjusted for age, race, and sex,[13] is compared with that observed in the general household population in this region.[14] Approximately three times more abstainers than would be expected are seen among both obstetric and gynecologic patients. However, almost as many heavy drinkers as expected are observed.

The proportions of women with various characteristics sometimes related to excessive alcohol use are presented according to age in Table III. Heavy drinking and alcohol-related problems are most prevalent among women age 30 to 39 years, with lower percentages among women who are younger or older, whereas the occurrence of physical and mental conditions sometimes associated with alcohol use tends to increase with age.

According to the summary screening score, which took into consideration all the data available from the screening program, 18% of the clinic population, 11% of the obstetric patients and 19% of the gynecologic patients were defined as probable or potential problem drinkers. Responses to questions about alcohol-related behavior asked in various parts of the screening program are summarized in Table IV. From 2% to 15% of the clinic population reported problems related to their own drinking; 26% reported that their parents had had drinking problems. Among women who were positive on screening, the percent reporting problems related to their own drinking ranged from 72% who were heavy drinkers to 8% whose relatives or friends had sought help for her drinking. Drinking problems among husbands, sibs, and children were not significantly correlated with positive screening scores in this population. The majority, from 59% to 100%, but not all, of the women who had specific problems related to their drinking also had positive scores on the screening program.

The Cage screening instrument was not administered by the examining physicians for 189 (38%) of the study subjects. In cases where the Cage questions were asked, there was a tendency for patients to deny alcohol-related behavior that they had previously reported on the self-administered questionnaire (see Table V). The converse also occurs; in 11 cases women denied a problem on the self-administered questionnaire and reported it to their physicians.

Of the 36 patients found by the alcoholism counselors to have no significant alcohol problem, 32 were

Table VII. Sensitivity and specificity rates for individual screening tests according to alcoholism counselors' diagnoses and summary screening score

Screening test	Positive on screening test (N = 499) (%)	Counsellors' diagnoses (N = 68)		Summary screening score (N = 499)	
		Sensitivity rate (%)	Specificity rate (%)	Relative* sensitivity rate (%)	Relative* specificity rate (%)
Self-administered screening test (N = 499):					
Two or more alcohol-related problems, plus heavy drinking (QFV or AA or VV)	10	56	97	50	99
Heavy drinking only (QFV and AA and VV—QFV or AA or VV)	9-16	59-84	94	50-65	100-95
Two or more alcohol-related problems only	32	56	97	75	77
Physician-administered "Cage" questions (N = 310) (positive responses to two or more of the four test questions)	3†	23	100	24	99
Blood alcohol concentrations (N = 62)	0	0	100	0	100
Review of medical record (N = 499)	5	13	100	25	85
Summary screening score (N = 499)	18	90	88		

*The summary screening score is treated here as a "truer" rather than a "true" measure of problem drinking; hence the terms relative sensitivity and specificity rates are used.

†Among the 310 patients who received this test 5% responded positively.

also so designated by the screening procedure, for an 88% specificity rate* (see Table VI). Of the 32 women identified as problem or potential problem drinkers by the counselors, only 14 scored as probable problem drinkers on screening, for a relatively low sensitivity rate of 44%. If potential and probable problem drinkers are combined, screening procedures identified 29 of the 32 patients also identified by the alcoholism counselors, for a 90% sensitivity rate.†

The percent sensitivity and specificity of the various components of the screening program as measured by comparison with diagnoses of the alcoholism counsellors and with the summary screening score are summarized in Table VII.

The high sensitivity rates indicate that most of the women who scored positively on the various screening tests were considered by the alcoholism counsellors to have significant alcohol-related problems. Positive scores on individual tests also tended to agree well with positive summary screening scores. However, the sensitivity rates of the individual and combined screening methods vary widely, from 0 in the case of blood alcohol concentrations, none of which were elevated, to 90% for the summary screening score. The physician-administered Cage questions and the medical record reviews identified 23% and 13%, respectively, of the probable and potential problem drinkers. Obviously, the summary screening score is not independent of the component parts of the screening program; however, the "relative" sensitivity and specificity rates provide an estimate of the usefulness of the component parts of the screening program in the total clinic population (see Table VII). Heavy drinking comes closest to identifying the same population as that selected by the summary screening score, combining as it does a fairly high relative sensitivity rate, 65%, with a high specificity rate, 95%.

The heavy use of alcohol is positively associated with several physical complaints commonly reported by the obstetric-gynecologic clinic patients, particularly among those under the age of 40: gastrointestinal pain ($P = 0.003$) and obesity ($P = 0.075$) (see Table VIII). There is a significant excess of heavy drinkers among women with one or more of the diseases or conditions sometimes associated with problem drinking ($P = 0.02$).

The etiologic contribution of heavy drinking to ill health cannot be accurately studied in individuals who already have a disease in which the use of alcohol is contraindicated since diagnosis of the disease may have prompted the individual to stop drinking. Thus, one would not expect to find large numbers of drinkers among patients with liver disease or diabetes; however,

*The *specificity* rate indicates the degree to which the screening test correctly identifies people with no significant alcohol-related problems.

†The *sensitivity* rate indicates the degree to which the screening test identifies women who are diagnosed as problem drinkers.

Table VIII. Relationship between drinking patterns and health in obstetric-gynecologic patients under age 40 years

Health conditions	*N*	*Drinking patterns*			*Significance level*
		Abstainers or infrequent drinkers (%)*	*Light or moderate drinkers (%)*	*Heavy drinkers* (%)*	
Gastrointestinal pain	52	25	40	35	0.003
Liver disease	4	50	25	25	N.S.
Anemia	9	11	67	22	N.S.
High blood pressure	15	40	27	33	N.S.
Obese	29	34	31	35	0.075
Trauma	23	30	39	30	N.S.
Seizure or convulsion	6	50	0	50	0.055
One or more physical complaints	136	35	40	26	0.023
One or more mental problems	30	27	40	33	0.070
Suicidal	11	18	46	36	N.S.
Totals		41 (157)	41 (156)	19 (72)	100% (385)

*According to QFV or AA or VV.

drinking is highly significant in those patients who do continue to use alcohol despite medical contraindications.

Pregnancy outcome for the obstetric patients according to the results of screening for alcohol-related problems is summarized in Table IX. Even in this relatively limited study, the difference in average birth weight between offspring of women with and without alcohol-related problems is statistically significant ($P = 0.04$, one-tailed t test) and clinically significant. A multiple regression analysis of the data indicated that maternal age accounted for approximately 1% of the variability in birth weight; the number of cigarettes smoked per day accounted for 1%; and the diagnosis of alcohol-related problems, entered last in the regression, accounted for 6% of the variability. Thus, the difference in birth weight cannot be attributed to maternal age or smoking habits. The occurrence of a stillbirth among the six women with probable or potential alcohol-related problems is consistent with the fetal problems expected in heavy-drinking women.

Comment

The high response rate obtained was very encouraging and indicates that obstetric-gynecologic patients will cooperate in studies of their alcohol use, at least in this setting. The question of "honest" answers is a more difficult one. There is little motivation for women to exaggerate their alcohol intake or to overreport alcohol-related problems; therefore, it is reasonable to suppose that the findings are accurate or are underestimates. While there are undoubtedly clinic patients who minimize their alcohol intake and deny alcohol-related problems, the striking aspect of the present findings is the fact that 18% of the clinic population reported drinking behavior with sufficient honesty to score as probable or potential problem drinkers.

A national survey found an incidence of high-level problem drinking which ranged from a high of 8% in women aged 30 to 39 years to a low of 1% in women over age 60 years.[15] The relationship between problem drinking and age reported in the nation is similar to that observed in the present study. The higher levels seen in the clinic support the suggestion that obstetric-gynecologic clinic patients are at high risk of alcohol-related problems; however, the national survey data are not directly comparable to those of the present study. Based on household interview data, women in the national survey were defined as problem drinkers with a score of seven or more (out of a possible 58) in 11 problem areas ranked according to the number and severity of problems experienced in the three years prior to the interview. No measures of physical or biochemical indicators of heavy alcohol use were available in the national survey. This factor plus the fewer number of problems required for a positive summary screening score in the present study may account in part for the higher levels of probable and potential problem drinkers identified by the screening procedures being tested here. Part of the differences may also be attributable to higher levels of heavy drinking among women in Western New York State compared to the United States as a whole.[14] Finally, individuals in the lower socioeconomic classes tend to report more problems associated with heavy alcohol use than do middle- and upper-class individuals.[16]

In comparing the sensitivity of various tests it was noted that physician-administered tests and review of

Table IX. The relationship of pregnancy outcome to alcohol-related problems as measured by screening in an obstetric-gynecologic outpatient clinic

Group	*Live births*	*Birth weight ±S.D. (grams)*	*Stillbirths*	*Induced abortion*	*Spontaneous abortion*	*Outcome not determined*	*Total*
No significant alcohol-related problems	49	3,166 ± 728	1	11	5	12	78
Probable or potential drinking problems	5	2,563 ± 567	1	1	0	3	10
Total	54	3,109 ± 732	2	12	5	15	88

the medical records identified far fewer probable and potential problem drinkers than did the self-administered questionnaire. This is consistent with previous reports that clients reported larger alcohol intakes in an impersonal, computer-mediated interview than in a person-to-person interview with a physician.[17] It may be that fear of physician censure may prompt women to minimize their alcohol use and related problems and that the self-administered questionnaire seems less threatening, leading to more accurate reporting of alcohol-related behavior. An alternative explanation is that the self-administered questionnaire raised the patients' anxiety levels and motivated denial in response to similar alcohol-related questions asked later by their physicians.

The sensitivity of the Cage screening instrument administered by the physician was also limited by the fact that 38% of the summary sheets were not returned. This may reflect an underlying reluctance on the part of some of the physicians to raise questions regarding alcohol-related problems with their patients on a routine basis. There are undoubtedly valid reasons for this: concern as to the time required, concern that the patient may be offended or less cooperative, and/or failure to remember to ask the question. Such issues may be partly overcome by use of the self-administered questionnaire.

The study findings offer some support for the hypothesis that heavy alcohol use is significantly related to the health of obstetric-gynecologic patients and their offspring, and further exploration of programs to screen routinely for alcohol-related problems in obstetric-gynecologic patients seems warranted. Additional reasons for continuing this research relate to the fact that women with alcohol-related problems tend to be missed by screening programs focused on the work place or on problems that occur outside the home, such as driving while intoxicated. This, plus access to data regarding physical signs and symptoms related to heavy alcohol use, puts the obstetrician-gynecologist in a unique position with respect to the diagnosis of alcohol-related problems in women. Women also tend to be seen in the obstetric-gynecologic setting at a time when they are concerned about their own health or that of their offspring, which may provide the motivation needed to initiate a change in harmful or potentially harmful drinking patterns.

Of particular interest would be trials of these and other screening tests in other regions of the United States and in other obstetric-gynecologic settings, such as private practices. In the longer view, the establishment of routine screening for alcohol-related programs in women must be supported by effective treatment programs. Clearly, there is much need for work in all these areas.

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Appendix A

The following diseases and conditions are sometimes related to excessive alcohol use:

1. Nausea
2. Gastrointestinal pain—ulcer, dyspepsia, gastritis
3. Tuberculosis
4. Liver disease—hepatomegaly, cirrhosis, hepatitis
5. Anorexia—weight loss
6. Anemia—iron deficiency
7. Dizziness
8. Numbness
9. Fatigue
10. Vocal cord granuloma
11. Obesity
12. Gout
13. Diabetes
14. Hypercholesterolemia
15. Coronary heart disease
16. High blood pressure
17. Repeated infections—colds, urinary tract, vagina
18. Rheumatic heart disease
19. Passing out
20. Neuropathy
21. Seizures
22. Convulsions
23. Difficulty sleeping
24. Trauma—assaults, falls
25. Dupuytrens contracture
26. Hyperflexia—upper extremities
27. Blackouts

*Counted as a major physical condition.

Appendix B

The following abnormal laboratory findings are sometimes associated with excessive alcohol use:

1. Hypoglycemia (serum glucose between 1 and 65 mg/dl)
2. Hyperglycemia (serum glucose over 110 mg/dl and not pregnant)
3. Low chloride (1 to 96 mEq/L)
4. High bicarbonate (30 mEq/L or over)
5. Low potassium (0.1 to 3.6 mEq/L)
6. Elevated serum glutamic oxaloacetic transaminase (34 μM/min. or over)
7. Elevated mean corpuscular volume (95 μ^3 or over)
8. Elevated lactic dehydrogenase (425 μM/min. or over)
9. Elevated alkaline phosphatase (86 μM/min. or over)
10. Elevated bilirubin (1.2 mg/dl or over)
11. Elevated white blood cell count (12×10^3 or over)
12. Low red blood cell count (0.1 to 3.9×10^6)
13. Elevated mean corpuscular hemoglobin (37 $\mu\mu$g or over)

Appendix C

The following mental conditions are sometimes associated with excessive alcohol use (the following conditions only contribute to the summary screening score if the patient reported heavy drinking on the self-administered questionnaire in addition to having mention of the mental condition in her medical record; the two were ascertained separately):

1. Depression
2. Nervousness
3. Anxiety
4. Crying
5. Insecurity
6. Fearfulness
7. Loneliness
8. Suicidal
9. Unable to cope (with family problems)
10. Poor personal hygiene
11. Dull/lack of intelligence
12. Mentally retarded
13. Sociopathic personality
14. Somatization
15. Hears voices
16. Malaise/lethargy/fatigue
17. Under stress
18. Depression/nervousness during pregnancy
19. Poor motivation for self help
20. Immature
21. Withdrawn
22. Neurotic
23. Psychiatric overlap
24. Overly emotional
25. Nervous breakdown
26. Inadequate personality
27. Underlying psychotic illness
28. Psychosis
29. Drug overdose*
30. Drop in libido
31. Dissatisfied life-style
32. Psychiatric disorder
33. Psychiatric illness

*Counted as a minor behavioral condition regardless of present level of alcohol use.

The influence of hypophysectomy, adrenalectomy, progesterone, oxytocin, and estradiol on the metabolic fate of ^{3}H-epinephrine in central and peripheral regions during late pregnancy

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Variations in the metabolic fate of ^{3}H-epinephrine during the last days of pregnancy were determined in seven peripheral organs and three brain regions of the rat. Hormonal treatments were performed during Days 19 to 21 after coitus. Hypophysectomy of the pregnant females on Day 17 after coitus increased the transformation of ^{3}H-metanephrine and ^{3}H-acid metabolites from tracer epinephrine when compared to Day 21 after coitus. Adrenalectomy produced effects similar to those of hypophysectomy as all the peripheral and central regions except the kidney showed an increased rate of ^{3}H-acid metabolite formation but the formation of ^{3}H-metanephrine was increased only in liver, spleen, ovary, uterus, hypophysis, hypothalamus, and brain. Pretreatment with oxytocin decreased the rate of amine metabolism in most of the organs. Progesterone increased the metabolism of tracer epinephrine in the heart, spleen, ovary, hypophysis, and hypothalamus. Estradiol treatment decreased metabolism of ^{3}H-epinephrine to ^{3}H-metanephrine and ^{3}H-acid metabolites in all of the peripheral and central regions with the exception of the hypothalamus. The rate of uptake of ^{3}H-epinephrine was extremely high in hypophysectomized pregnant rats and very low in progesterone-treated females. Results suggest that steroid and peptide hormones play an important role in the control of monoaminergic function during late pregnancy. (AM. J. OBSTET. GYNECOL. 134:13, 1979.)

THE EXACT role of catecholamines in the maintenance and termination of pregnancy has been studied by several authors during the past decade. The consequences of natural variations in epinephrine, norepinephrine, and related metabolites differ from one animal species to another one.[1] More recently the role of endocrine gland secretions in the processes of monoamine synthesis and release and metabolism during the estrus cycle and pregnancy has become a subject of great interest, and it seems certain that the activity of monoaminergic function depends directly on normal neuroendocrine activity.[2, 3] Our recent studies in rats and rabbits during the estrus cycle, pregnancy, and parturition show a direct link between termination of pregnancy and evolution of adrenal and plasma epinephrine and norepinephrine.[3, 4] It was also found that natural variations in transmitter concentrations which occur during pregnancy and parturition result from modifications in steroid hormone concentrations.[4, 5] In a previous study we showed that the uptake and metabolism of exogenously administered ^{3}H-epinephrine is greatly modified during different days of the last trimester of pregnancy in peripheral and central organs.[5] The variations in physiologic accumulation of ^{3}H-epinephrine and its transformation to ^{3}H-metanephrine and ^{3}H-acid metabolites during the last days of pregnancy which we observed on the eighteenth and twenty-first days after coitus and at 0 hour post partum

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Table I. The metabolic fate of exogenously administered ^{3}H-epinephrine in the blood, heart, kidney, and brain after different intervals of perfusion of the tracer. Counts per minute per liter or counts per minute per unit weight of the organ show total radioactivity found at each specific interval

Post perfusion time (min.)	*Blood (cpm/L)*	*Heart (cpm/100 mg)*	*Kidney (cpm/100 mg)*	*Brain (cpm/gm)*
2	3,010	14,220	9,000	7,200
20	1,457	9,760	8,600	6,860
120	560	4,896	1,936	6,900

could be correlated with natural modifications of steroid hormonal concentrations.[6]

The present study shows the effects of two days of pretreatment with oxytocin, progesterone, and estradiol upon the metabolic fate of ^{3}H-epinephrine administered on the twenty-first day of pregnancy. The pregnant rats were also hypophysectomized or adrenalectomized on the seventeenth day of pregnancy and the effects of these surgical hormone alterations on metabolism and uptake of ^{3}H-epinephrine were compared with that of nontreated animals.

Material and methods

Albino female rats of Sherman strain were used in all experiments. The weight of the rats ranged from 300 to 350 grams. The animals were housed at a temperature of 21° ± 1° C with exposures to natural light and darkness. The females were impregnated by keeping one male in the cage of seven females from 7 P.M. to 9 A.M. only once. The fertilization was supposed to occur at 2 A.M. This made it possible to estimate the beginning of pregnancy ±7 hours. The females were palpated 14 days later for verification of pregnancy. If they were found to be pregnant, at 2 P.M. they were considered to be 14.5 days pregnant. Under normal conditions parturition took place during 21.5 to 22 days of pregnancy.

Hormone administration, hypophysectomy, and adrenalectomy. The females on Days 19, 20, and 21 after coitus were injected with progesterone retard, Schering, Berlin (6 mg/100 gm subcutaneously) or estradiol retard, Schering, Berlin (0.65 mg/100 gm). Oxytocin (Choay, Paris, France) (1.25 IU/100 gm) was injected only twice on Days 20 and 21 after coitus. The pregnant females on Day 17 after coitus were either hypophysectomized or adrenalectomized under ether anesthesia. The adrenalectomized rats received 0.9% saline for drinking.

^{3}H-epinephrine administration. ^{3}H-DL-epinephrine (specific activity 4 Ci/mM) was obtained from the Centre D'Energie Atomique, Gif Sur Yvette, France, in ampules each containing 1 mCi of ^{3}H-epinephrine as 0.2N acetic acid solution. The contents of each ampule were diluted to 3.33 ml with twice-distilled water at pH 3. On the twenty-first day of gestation the diluted tracer was further mixed with 0.9% saline and perfused intravenously through a saphenous vein. Each rat was perfused with 60 μCi of ^{3}H-epinephrine under light ether anesthesia. The perfusion lasted for one minute. The disappearance of radioactivity in blood, heart, kidney, and brain was determined at various intervals after perfusion to find out the most suitable period with appreciable amount of radioactivity in most of the organs studied (Table I). Twenty minutes was found to be the best time for all comparisons as a significant amount of tracer was present in hypophysis, hypothalamus, and brain at this interval. Previous studies on the metabolic fate of ^{3}H-epinephrine by Axelrod and associates[7] also show a choice of about a similar interval as that used by us. The main aim of the present experiments was to find differences in ^{3}H-epinephrine accumulation and metabolism in pregnant rats subjected to different hormonal treatments. This is why all the comparisons in all the tissues have been made at 20 minutes postperfusion period. Moreover, the rate of disappearance of radioactivity at 2, 20, and 120 minutes after perfusion was the same in the brain and kidney. This was taken as supplementary evidence to limit our study to only one time interval. All of the animals were killed by neck fracture 20 minutes after the perfusion and the tissues were excised immediately, weighed, and transferred to tubes containing 8 ml of ice-cold mixture of 4% trichloroacetic acid plus 1% EDTA. The homogenization was performed in a Sorvall Omni Mixer. The homogenates were centrifuged immediately at 7,000 × g for 10 minutes. The supernate was divided into three portions: 1 ml each for ^{3}H-metanephrine and ^{3}H-acid metabolites and 3 ml for ^{3}H-epinephrine.

Estimation of ^{3}H-epinephrine. ^{3}H-epinephrine in the supernate was assayed by the method of Euler and Lishajko[8] by adsorption on acid-activated aluminium oxide with preference of batch process to columns.[8] The supernate from all organs in a volume of 3 ml was placed in a 5 ml beaker and 0.5 gm of aluminium oxide was added. The extract was placed on a magnetic stirrer, diluted with sodium acetate, 0.2M at pH 8.4, and adjusted to pH 8.4 first with 1N NaOH and finally with 0.01N NaOH. The operation was controlled by a direct-reading pH meter. The suspension was stirred for

three minutes for adsorption of tritiated epinephrine on alumina and centrifuged afterward for three minutes at 5,000 × g. The supernate was discarded and the precipitate was washed with 5 ml of twice-distilled water. After centrifugation for 3 minutes at 5,000 × g, the ^{3}H-epinephrine was eluted with 2 ml of 0.25N acetic acid. The elutes containing ^{3}H-epinephrine were further centrifuged for five minutes at 8,000 × g to spin down the smallest particles of alumina. The aliquot in volume of 0.5 ml was added to a vial containing 10 ml of Bray's phosphor prepared in dioxane. The vials were counted in a liquid scintillation counter for 10 minutes. The extracted counts per minute show direct linearity with the eluted ^{3}H-epinephrine. The recovery was in the range of 75% to 80%. The results have been corrected for this loss.

Determination of ^{3}H-metanephrine. After addition of 0.1 ml of concentrated HCl to 1 ml of supernate of the tissues, the pH of the mixture was adjusted to 10 to 10.5 with 5N NaOH and 1 ml borate buffer at pH 10. Metanephrine was extracted into 3.5 ml of a toluene and isoamyl alcohol (3 : 2) mixture by mechanical shaking for 30 minutes.[7] After centrifugation, a 3 ml aliquot of the extract was transferred to a vial containing 1 ml absolute ethyl alcohol and 10 ml Bray phosphor. The radioactivity was counted for 10 minutes. On these conditions, about 51% metanephrine was extracted into the organic phase. All the values reported are corrected.

Determination of ^{3}H-acid metabolites. One-tenth volume of 1N HCl was added to 1 ml of tissue supernate in a hemolyse tube and extracted with 3.5 ml of isoamyl alcohol.[7] The aqueous phase was removed by aspiration and the extract was washed with 0.5 ml of 0.1N HCl. A 3 ml aliquot of isoamyl alcohol extract was transferred to a vial containing 1 ml of absolute ethanol and 10 ml of Bray phosphor prepared in toluene. The radioactivity was measured in a liquid scintillation counter for 10 minutes. Both 3,methoxy-4-hydroxymandelic acid and 3,4-dihydroxymandelic acid are extracted and measured by this procedure. The recovery was in the range of 60% and the values were corrected for this loss.

Results

Table II shows physiologic accumulation of exogenously administered ^{3}H-epinephrine to pregnant females. Estradiol pretreatment from 19 to 21 days after coitus increased physiologic accumulation of labeled epinephrine in the ovary, uterus, hypothalamus, and liver but the heart, kidney, spleen, adrenals, hypophysis, and the rest of the brain demonstrated a decrease in this accumulation. All the peripheral organs, hypophysis, and the rest of the brain showed decreased rate of ^{3}H-epinephrine accumulation after pretreatment of pregnant females with progesterone. Similar pretreatment of progesterone increased ^{3}H-epinephrine accumulation in the hypothalamus. The preadministration of oxytocin to pregnant females resulted in decreased accumulation of radioactive epinephrine in liver, kidney, adrenals, uterus, hypophysis, hypothalamus, and the rest of brain and decrease in heart, spleen, and ovary. Hypophysectomy of pregnant females at 17 days after coitus produced marked increases in the accumulation of ^{3}H-epinephrine of all the peripheral organs and central regions. The effects of adrenalectomy of pregnant females were different for each organ concerned. After adrenalectomy the heart, liver and hypothalamus showed increase and the kidney, spleen, ovary, hypophysis, and the rest of the brain showed decrease in physiologic accumulation of ^{3}H-epinephrine.

The metabolic transformation of exogenously administered ^{3}H-epinephrine to ^{3}H-metanephrine has been provided in Table III. The effects of hypophysectomy of the pregnant females were more marked than any treatment as all the peripheral and central organs showed an increase in transformation of ^{3}H-epinephrine to ^{3}H-metanephrine. Adrenalectomy also produced effects similar to hypophysectomy as all the organs except the heart and the rest of the brain showed an increase in metabolic transformation of the labeled amine. Estradiol injection from 19 to 21 days after coitus resulted in decreased conversion of ^{3}H-epinephrine to ^{3}H-metanephrine in the heart, liver, kidney, spleen, adrenals, ovary, uterus, hypophysis, and the rest of the brain. Hypothalamus was the only brain region which demonstrated an increase in ^{3}H-metanephrine transformation after estradiol pretreatment of pregnant females. Progesterone treatment to pregnant females resulted in increased formation of ^{3}H-metanephrine in the heart, spleen, ovary, and hypothalamus, but the liver, kidney, adrenals, uterus, hypophysis, and the rest of the brain showed a decreased rate of ^{3}H-metanephrine formation from ^{3}H-epinephrine. Pretreatment of pregnant females with oxytocin produced a decreased rate of this metabolic conversion in all of the organs except the hypophysis and hypothalamus. Table IV provides a comparison between the effects of different hormonal treatments during 17 to 21 days after coitus upon metabolic transformation of exogenously administered ^{3}H-epinephrine to ^{3}H-acid metabolites. Again the effects of each hormonal treatment were well specified in peripheral

Table II. ^{3}H-epinephrine

Treatment	Heart (cpm/100 mg)	Liver (cpm/100 mg)	Kidney (cpm/100 mg)	Spleen (cpm/100 mg)	Adrenal (cpm/100 mg)	Ovary (cpm/100 mg)
Pregnant 21 days	14,168	5,950	4,345	5,569	8,911	4,647
Estradiol 19-21 days	11,614	9,370	3,621	4,902	7,157	5,178
Progesterone 19-21 days	9,795	5,879	3,380	3,491	5,956	4,297
Oxytocin 19-21 days	22,695	3,692	3,862	8,336	8,506	5,871
Adrenalectomy 17-21 days	16,878	8,401	3,893	3,838	XXXXXXX XXXXXXX	4,199
Hypophysectomy 17-21 days	20,733	8,276	7,269	7,191	11,985	6,827

Each group consists of at least five to six determinations. The results were homogenous and any difference above or below 10% should be considered significant.

Table III. ^{3}H-metanephrine

Treatment	Heart (cpm/100 mg)	Liver (cpm/100 mg)	Kidney (cpm/100 mg)	Spleen (cpm/100 mg)	Adrenal (cpm/100 mg)	Ovary (cpm/100 mg)
Pregnant 21 days	7,198	1,347	8,236	1,955	5,488	5,615
Estradiol 19-21 days	6,835	1,141	5,149	1,847	4,978	5,159
Progesterone 19-21 days	8,295	1,244	5,919	2,030	5,429	5,728
Oxytocin 19-21 days	6,316	1,068	5,434	1,617	4,782	5,208
Adrenalectomy 17-21 days	6,507	1,494	5,659	1,964	XXXXXXX XXXXXXX	6,590
Hypophysectomy 17-21 days	9,476	1,979	10,348	2,949	10,633	8,285

The mean value for each tissue consists of at least five to six individual determinations. The maximum difference between individual results was ±8%. Any difference above or below this value should be taken as a significant effect.

Table IV. ^{3}H-acid metabolites

Treatment	Heart (cpm/100 mg)	Liver (cpm/100 mg)	Kidney (cpm/100 mg)	Spleen (cpm/100 mg)	Adrenal (cpm/100 mg)	Ovary (cpm/100 mg)
Pregnant 21 days	10,952	2,574	13,949	3,366	8,071	6,072
Estradiol 19-21 days	10,246	1,861	6,517	3,346	6,398	5,065
Progesterone 19-21 days	11,124	2,409	7,147	4,039	7,118	6,233
Oxytocin 19-21 days	9,586	2,036	7,352	3,293	5,867	5,270
Adrenalectomy 17-21 days	12,734	3,164	8,316	4,336	XXXXXXX XXXXXXX	6,906
Hypophysectomy 17-21 days	15,991	3,672	16,166	7,029	10,259	7,177

Each group consists of a mean of at least five to six individual determinations from different animals. The maximum variation between individual results ranged from 8 to 10%. Therefore, any change below or above this value should be taken as significant.

as well as central organs. Hypophysectomy of the pregnant females resulted in increased metabolism of exogenously administered ^{3}H-epinephrine to ^{3}H-acid metabolites in all of the peripheral organs and three brain regions. Adrenalectomy also produced increased formation of ^{3}H-metabolites from nontreated values in heart, liver, spleen, adrenals, ovary, uterus, hypophysis, hypothalamus, and brain but the kidneys were the only organs which showed a decreased rate of metabolism to ^{3}H-acid metabolites. Estradiol pretreatment resulted in decreased formation of ^{3}H-acid metabolites in all the peripheral organs, hypophysis, and

Uterus (cpm/100 mg)	*Hypophysis (cpm/100 mg)*	*Hypothalamus (cpm/100 mg)*	*Rest of brain (cpm/100 mg)*
805	8,384	1,645	108
897	5,518	2,128	95
623	6,024	1,975	105
741	6,885	1,567	102
805	7,884	1,761	95
1,135	XXXXXX XXXXXX	2,077	166

Uterus (cpm/100 mg)	*Hypophysis (cpm/100 mg)*	*Hypothalamus (cpm/100 mg)*	*Rest of brain (cpm/100 mg)*
1,808	15,670	3,880	494
1,607	12,612	4,864	450
1,597	14,959	4,503	455
1,342	15,880	4,934	445
1,832	22,510	5,448	592
2,445	XXXXXX XXXXXX	5,772	686

Uterus (cpm/100 mg)	*Hypophysis (cpm/100 mg)*	*Hypothalamus (cpm/100 mg)*	*Rest of brain (cpm/100 mg)*
2,069	11,434	3,197	551
1,732	9,985	3,498	475
1,722	12,302	3,606	504
1,432	10,652	3,144	448
2,184	13,978	3,834	653
2,699	XXXXXX XXXXXX	3,870	755

the rest of the brain but the hypothalamus showed a decrease in this metabolic transformation. The effects of oxytocin pretreatment were very similar in all the peripheral and central regions as all the tissues showed a decreased rate of ^{3}H-acid metabolite formation from the value of nontreated females. Progesterone administration during 19 to 21 days after coitus increased ^{3}H-acid metabolite formation in the heart, spleen, ovary, hypophysis, and hypothalamus and decreased this formation in the liver, kidney, adrenals, uterus, and the rest of the brain.

Comment

The results of the present investigation show the influence of different hormones and ablation of the hypophyseoadrenocortical system upon processes of monoamine accumulation and metabolic degradation. The effects of progesterone, estradiol, and corticoids upon enzymes of monoamine synthesis and metabolism have been well investigated in normal males and females during the proestrus phase of the estrus cycle.[9, 10] It was found that the effects of these hormones differ to a marked extent according to the physiologic state of the animal.[9, 10] From Tables III and IV it is evident that hypophysectomy and adrenalectomy produce an increased rate of ^{3}H-metanephrine and ^{3}H-acid metabolite formation from ^{3}H-epinephrine. These observations support our previous findings about the role of adrenal glucocorticoids in the maintenance of enzymes monoamine oxidase and catechol-O-methyltransferase. We found that hypophysectomy or adrenalectomy of the adult or fetus results in highly marked and significant increases in the activities of the enzymes monoamine oxidase and catechol-O-methyltransferase in central and peripheral regions.[11] The inhibition of glucocorticoid biosynthesis pharmacologically by pretreatment of metopirone also results in an increased rate of monoamine metabolism.[9]

The administration of estradiol resulted in decreased transformation of ^{3}H-epinephrine to ^{3}H-metanephrine and ^{3}H-acid metabolites in most of the tissues studied. This observation is in agreement with the previous findings about the action of estradiol upon the activity of enzyme monoamine oxidase in cyclic females,[2] as it was found that estradiol inhibits oxidative deamination of monoamines. The pretreatment of progesterone was followed by increases in some tissues and decreases in the other tissues for the process of ^{3}H-acid metabolite and ^{3}H-metanephrine formation. Under normal conditions the administration of progesterone to animals during the estrus cycle results in increased activity of enzyme monoamine oxidase[2] but in a recent study[10] we have shown that this specific action of progesterone to increase the monoamine oxidase activity during the estrus cycle was limited to that specific period only and was dependent upon the ratio of free and bound progesterone. During pregnancy when the natural concentration of progesterone varies to a great extent, the administration of progesterone to pregnant females results in decreased activity of enzyme monoamine oxidase.[10] Oxytocin, which is a neurohypophyseal hormone, acts like estradiol for the metabolism of ^{3}H-epi-

nephrine to ^{3}H-acid metabolites and ^{3}H-metanephrine since the pretreatment of this hormone also resulted in an increased rate of monoamine metabolism. ACTH which is also a neurohypophyseal hormone has an important action on the formation of epinephrine in the adrenal medulla. It was shown that normal function of the adrenal cortex which is maintained by circulating ACTH was essential for the induction of enzyme phenylethanolamine-N-methyltransferase in the adrenal medulla.[12] The lack of ACTH decreases adrenal epinephrine stores and increases related metabolites of monoamines.[12, 9]

The physiologic accumulation of tracer epinephrine varied according to specific treatment and specific tissue. The effects of hypophysectomy were very uniform as all the organs showed decreased accumulation of ^{3}H-epinephrine whereas ocytocine and progesterone pretreatments produced a decreased rate of epinephrine uptake. These differences can be better interpretated if we look into the extensive studies of Iversen.[13] The role of steroid hormones in the processes of catecholamine uptake was also shown recently and it is certain that the rate of amine uptake by a tissue depends upon the intensity of its adrenergic innervation; its histologic status is more valid for the study of uptake kinetics under controlled experimental conditions in vitro.[13] Now it is accepted that the process of uptake$_2$ has a great importance for physiologic accumulation of amines.[13] Uptake of catecholamines by this process is rapidly followed by intracellular catabolism; uptake$_2$ could thus constitute a mechanism for disposing of extracellular catecholamines by an "uptake and followed by metabolism" process, as opposed to classical "uptake and retention" mechanism previously described by Iversen[13] as uptake$_1$. By uptake$_2$ mechanism, the amines are also taken up by a different transport system in various extraneuronal peripheral tissues, such as vascular smooth muscle, cardiac muscle, and certain glandular tissues. In the isolated rat heart, catecholamines are taken up by two uptake processes, distinguishable because of their different kinetic and pharmacologic properties.[13] It seems that the uptake$_2$ process has a lot to do for the regulation of epinephrine metabolism during pregnancy but it still remains a suggestion as in the present study uptake$_1$ and uptake$_2$ were not differentiated. The presence of an extraneuronal uptake mechanism similar to uptake$_2$ process has also been shown in the recent years which can be taken as an important factor for the variations which we observe in different organs to different hormonal pretreatments.

From the present findings it can be assumed that the processes of monoamine accumulation and metabolism can be markedly modified by exogenous administration of different hormones during late pregnancy. Most of the modifications observed follow well-established action of steroid and peptide hormones on the processes of amine uptake and metabolism. These observations provide some biochemical interpretation of the findings of Zuspan and colleagues[14, 15] in human beings about the role of monoaminergic activity in the maintenance of pregnancy.

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Maternal and fetal renin activity and renin and big renin concentrations in second-trimester pregnancy

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Plasma renin activity (PRA) and the concentrations of renin (PRC) and big renin (PBRC) have been determined in maternal and fetal blood, and renin and big renin have been measured in amniotic fluid, at 16 to 20 weeks of gestation. Gradients between peripheral arterial and venous and uterine venous maternal circulation were not apparent for PRA, PRC, or PBRC. PRC and PBRC but not PRA were consistently higher in fetal cord blood than in the maternal compartment. The concentrations of big renin and of renin were tenfold higher in amniotic fluid than in maternal plasma and were significantly correlated in amniotic fluid but not maternal or fetal plasma. (AM. J. OBSTET. GYNECOL. 134:20, 1979.)

IN THE STUDY of maternal-fetal endocrine relationships, hormonal gradients within the maternal circulation and between mother and fetus have established interdependence and independence of the maternal and fetal compartments. Despite studies at various gestational ages of many aspects of endocrine function, data pertaining to maternal and fetal levels of plasma renin activity (PRA) and concentration (PRC) have been limited to term pregnancy,[1-6] and comparable studies from earlier in pregnancy have not been previously reported.

Big renin has been identified in maternal plasma,[7] in amniotic fluid,[7] and in the plasma of normal newborn infants,[8] but possible gradients of plasma big renin concentration (PBRC) within the maternal circulation or between maternal and fetal compartments have not been studied.

In the current study, PRA, PRC, and PBRC have been measured at 16 to 20 weeks from simultaneous samples of the maternal venous and arterial circulation and in paired maternal and fetal blood specimens. In addition, concentrations of renin and big renin have been determined in paired samples of maternal plasma and amniotic fluid.

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Material and methods

The protocol for the study was approved by the Institutional Review Board and informed written consent was obtained from all subjects. The 13 subjects were undergoing elective termination of 16 to 20 week pregnancies for psychosocial indications, and the subjects' decisions for termination of pregnancy were made with medical personnel not involved in the study.

Nine subjects underwent abortion-hysterectomy. Antecubital and uterine venous samples were obtained from seven; a radial arterial sample was obtained from one of this group. In one patient, radial arterial and uterine venous samples were obtained, and in one only an antecubital venous sample was obtained. Amniotic fluid was obtained from two subjects. All specimens were obtained immediately prior to removal of the uterus. Fetal blood was obtained in four instances.

Four subjects had therapeutic abortion by intra-amniotic urea-prostaglandin instillation. Samples of antecubital venous blood and of amniotic fluid were obtained immediately prior to the procedure.

Plasma renin activity and the concentrations of renin and big renin (total renin concentration following activation by pH 3.3 and incubation with trypsin, minus the renin concentration) were determined by methods previously described[9] and results expressed as nanograms per milliliter per hour of generated angiotensin I.

Results

Shown in Table I are the results for determinations of PRA, PRC, and PBRC in seven paired samples of peripheral and uterine venous plasma. Mean (±SD)

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Table I. Maternal venous PRA, PRC, and PBRC (nanograms per milliliter per hour of angiotensin I)

No.	*PRA*		*PRC*		*PBRC*	
	Peripheral	*Uterine*	*Peripheral*	*Uterine*	*Peripheral*	*Uterine*
1	9.1	6.3	24.4	9.2	36.3	46.8
2	6.5	6.1	13.0	9.4	33.1	30.1
3	4.2	5.8	7.8	9.6	47.8	78.4
4	8.5	6.9	12.9	12.5	27.7	27.2
5	12.8	10.8	18.6	15.7	113.3	110.4
6	8.8	8.4	22.6	17.9	16.7	16.5
7	3.8	8.0	25.9	27.9	141.7*	—
Mean	7.7	7.5	17.9	14.6	45.8	51.6
S.D.	2.9	1.6	6.3	6.3	31.6	32.9

*Not included in mean.

Table II. Maternal arterial and venous and fetal cord blood PRA, PRC, and PBRC (nanograms per milliliter per hour of angiotensin I)

No.	*Plasma renin activity*				*Plasma renin concentration*				*Plasma big renin concentration*			
	Peripheral		*Uterine venous*	*Cord blood*	*Peripheral*		*Uterine venous*	*Cord blood*	*Peripheral*		*Uterine venous*	*Cord blood*
	Arterial	*Venous*			*Arterial*	*Venous*			*Arterial*	*Venous*		
1	6.0	6.5	6.1	22.7	11.4	13.0	9.4	63.7	26.9	33.1	30.1	38.0
2	23.5	—	28.6	42.5	26.9	—	20.6	126.0	49.3	—	44.6	184.3
3	—	15.0	—	9.9	—	25.8	—	38.4	—	133.8	—	210.0
4	—	3.8	8.0	—	—	25.9	27.9	47.3	—	141.7	—	228.9
				5.8*				41.7*				113.3*

*Cardiac blood.

values for PRA (7.7 ± 2.9 versus 7.5 ± 1.6) and PRC (17.9 ± 6.3 versus 14.6 ± 6.3) are slightly higher and for PBRC (45.8 ± 31.6 versus 51.6 ± 32.9) are slightly lower in peripheral blood, but the differences are not statistically significant ($p > 0.1$, Student's t test).

In Table II are shown the results of determinations of PRA, PRC, and PBRC in the maternal and fetal circulations. Again, consistent gradients within the maternal circulation are not evident. Although values for PRA are variable, in each instance PRC and PBRC are higher in fetal cord blood than in both arterial and venous maternal plasma. In one fetal subject, cord blood PRC was slightly higher and PBRC twofold higher than in cardiac blood.

Shown in Table III are results for determinations of maternal venous PRC and PBRC and for renin and big renin concentrations in amniotic fluid in six paired specimens. Values for renin concentration in amniotic fluid are fourfold to 24-fold higher (mean, 10.4 not shown) and for big renin, fourfold to 36-fold higher (mean, 10.8, not shown) than in maternal plasma.

The mean (±SD) ratios of big renin:renin (not shown) in maternal plasma (4.7 ± 4.6), cord plasma (3.1 ± 2.1), and amniotic fluid (3.4 ± 1.4) were not significantly different ($p > 0.1$). Determinations of correlation coefficients revealed significant correlation of

Table III. Maternal venous and amniotic fluid renin and big renin concentrations (nanograms per milliliter per hour of angiotensin I)

No.	*Renin concentration*		*Big renin concentration*	
	Maternal venous	*Amniotic fluid*	*Maternal venous*	*Amniotic fluid*
1	8.3	76.8	7.7	274.2
2	14.2	373.0	157.2	1194.5
3	8.9	136.8	189.1	856.8
4	8.2	46.8	24.8	145.1
5	24.4	92.0	36.3	169.6
6	13.0	55.9	33.1	138.4
Mean	12.8	130.2	72.4	463.1
S.D.	5.7	112.4	72.3	412.0

the concentrations of big renin and renin in amniotic fluid (r 0.9075; $p < 0.01$) but not in maternal (r 0.1780; $p > 0.1$) or cord blood (r 0.0959; $p > 0.1$).

Comment

In previously reported studies of full-term pregnancies, maternal peripheral arterial[1] and venous[2] PRA have been slightly higher and PRC slightly lower[3] than in uterine blood. As in the current report, where both PRA and PRC were higher in peripheral venous blood, the differences were not satistically significant. The

available data therefore suggest that gradients of PRA and PRC within the maternal circulation do not occur consistently in pregnancy either at 16 to 20 weeks or at term.

Studies of maternal and fetal PRA and PRC at term have yielded variable results.[3] Although higher maternal[4] or fetal[5] PRA has been reported, the method of delivery may partially account for the observed differences.[6] In the current study, fetal PRC (but not PRA) at 16 to 20 weeks gestation was consistently greater than maternal values.

Big renin presumably originates during pregnancy from fetal chorion[3] and has been found in maternal plasma throughout gestation,[7] in amniotic fluid,[7] and in plasma of newborn infants.[8] In the current study the highest concentrations of big renin occurred in amniotic fluid and PBRC was consistently higher in the fetal than in the maternal circulation. Additionally, in one fetal subject, PBRC from cord blood was higher than that from cardiac blood. These observations are compatible with a fetal chorionic source of big renin.

The ratios of big renin to renin in maternal plasma and in amniotic fluid at 16 to 20 weeks in this report are comparable to those previously reported.[7] The positive correlation of big renin and renin concentrations in amniotic fluid at 16 to 20 weeks and at 34 to 37 weeks,[7] but not in maternal or fetal plasma, suggests that factors which control the relative concentration of each in amniotic fluid are different from those in the maternal and fetal circulations.

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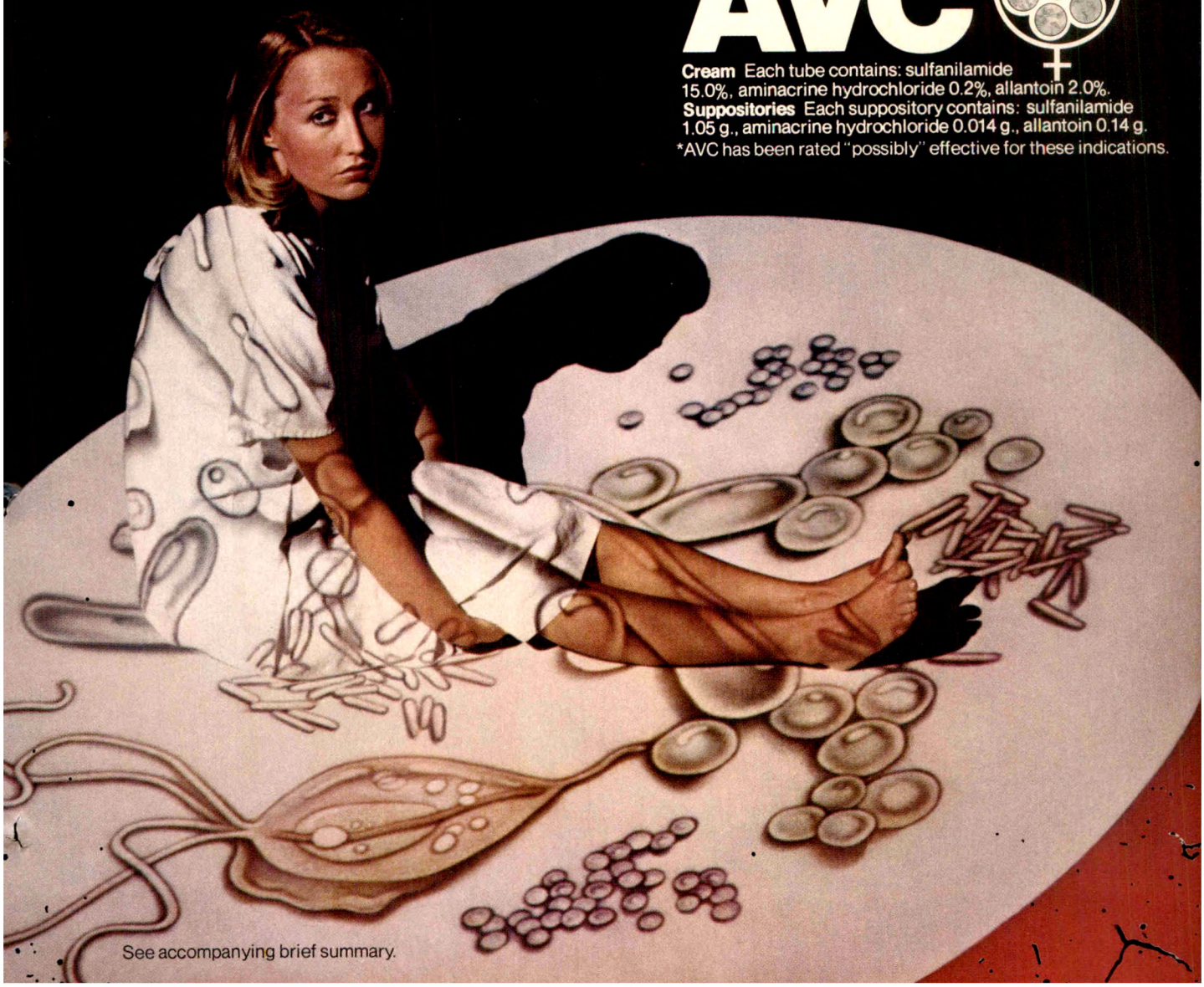
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- Product Information as of January, 1978

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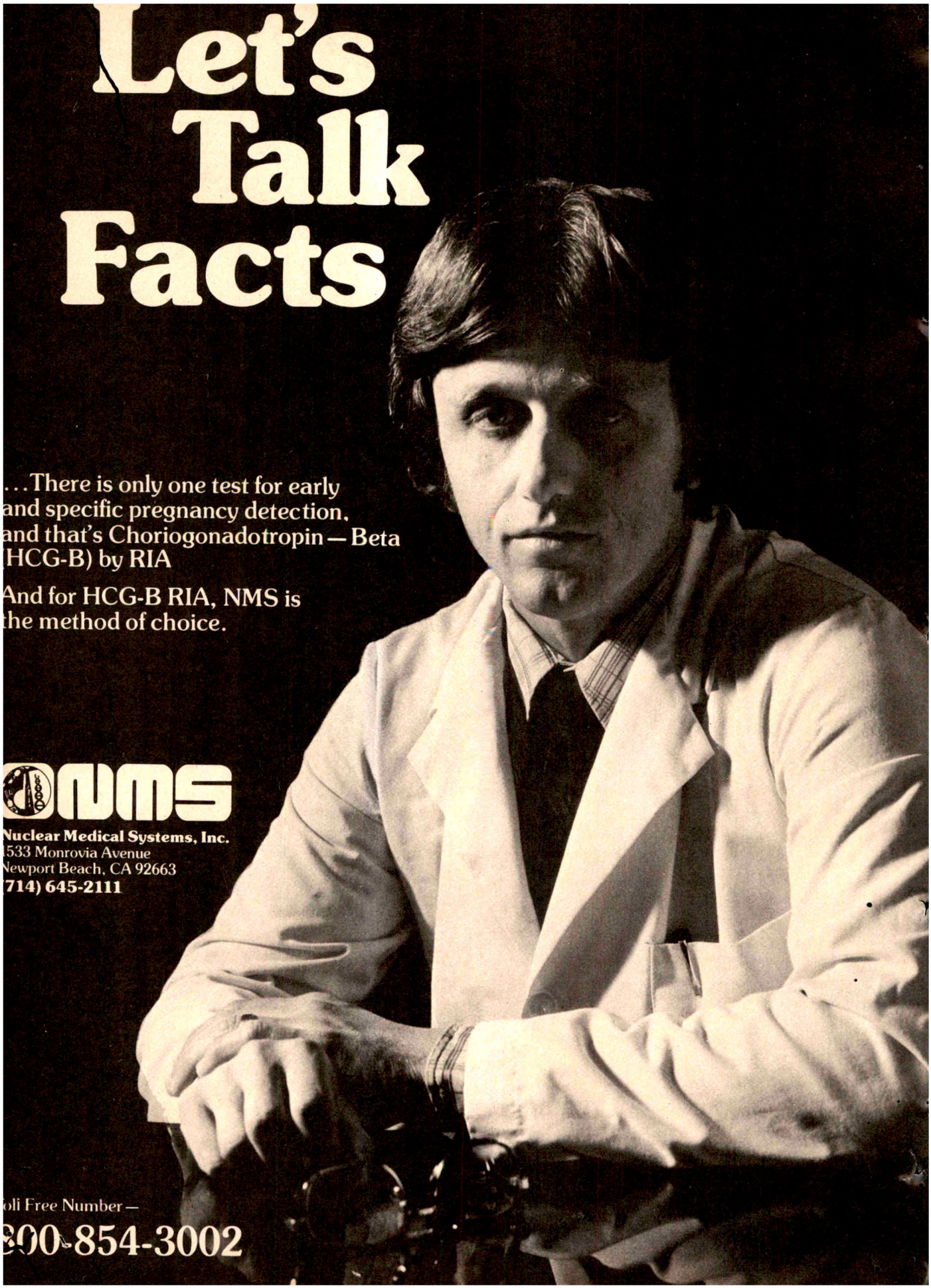
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FETUS, PLACENTA, AND NEWBORN

Bed rest in twin pregnancy: Identification of a critical period and its cost implications

WILLIAM F. POWERS, M.D., M.P.H.
TIM C. MILLER, M.D.
Peoria, Illinois

Since twin pregnancies often result in poor perinatal outcomes, many physicians advise prolonged bed rest. Recommendations concerning the timing of bed rest conflict and are made with little assessment of costs. This review of twin pregnancies in the North Central Illinois perinatal region establishes that twins are most vulnerable if they are born between 27 and 34 weeks' gestation. If bed rest is to be imposed, it probably should be timed so as to influence this vulnerable period. Intervention (bed rest in the hospital from 27 to 34 weeks' gestation) would cost between $5,720 and $6,909 per twin pregnancy, whereas nonintervention (intensive care nursery charges for infants born before 34 weeks' completed gestation) would cost $1,689 per twin pregnancy. Before intervention can be universally advocated and costs of this magnitude incurred, a prospective controlled trial to determine the efficacy of bed rest in twin pregnancy is mandatory. (AM. J. OBSTET. GYNECOL. 134:23, 1979.)

MULTIPLE pregnancies are associated with high morbidity and mortality rates. Approximately 55 per cent of twins born in the United States weigh less than 2,500 grams at birth, and about 40 per cent of twins are born before 37 weeks' gestation. The mortality rate of twins is about four times that of singletons. In addition, twins more frequently have long-term problems such as short stature, delayed mental development, and cerebral palsy.[1] Data collected in an era of neonatal intensive care perhaps indicate a slight improvement in the prognosis for twin pregnancies,[2] but still twinning remains a very high-risk situation.[3]

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Since the preponderance of risks associated with twin pregnancy are related to premature delivery,[2, 4] many recommend prolonged bed rest to avoid early delivery[5–11] even though the efficacy of bed rest still remains unproved.[1, 3, 12–16] The clinician contemplating bed rest for his patient pregnant with twins unfortunately discovers no consensus as to when bed rest should be started or stopped. In fact, recommendations are contradictory. Some suggest or report starting bed rest in the hospital as early as 25 to 28 weeks' gestation[10, 13] or as late as 35 to 36 weeks' or later.[17–19] Bed rest is discontinued as early as 34 weeks' gestation[14, 20] or as late as possible.[13, 18] Thus, some suggest stopping bed rest as early as two weeks before others recommend starting.

Analysis of the recent experience with twin pregnancies in the North Central Illinois perinatal region delineates a fairly discrete "critical period" during which early delivery is associated with high morbidity and mortality rates. During this time bed rest might be

Table I. Peoria twin data 1974 to 1977

Gestational age (wk.)	*Total births*	*Admitted to NICU*	*Survivors*	*Total NICU cost ($)*	*Total routine cost ($)*	*Cost per survivor ($)*
<28	18*	8	0	53,869		—
28	8	8	2	33,269		16,635
29	4†	2	2	16,908		8,454
30	4	4	2	30,219		15,110
31	4	4	3	22,198		7,399
32	18	18	18	102,082		5,671
33	14	14	12	47,322		3,944
34	22	22	21	62,392		2,971
Subtotal ≤ 34	92	80	60	368,259		$\bar{X}$ = 6,138
35	20	16	19	38,525	2,106	2,138
36	34	16	34	17,615	11,052	843
37	34	6	34	10,758	20,020	905
≥ 38	256‡	17	251	4,236	100,282	416
Subtotal ≥ 35	344	55	338	71,134	133,460	$\bar{X}$ = 605
Grand total	436	135	398	439,393	133,460	$\bar{X}$ = 1,439

NICU = neonatal intensive care unit.

*Includes six stillbirths and four infants not resuscitated in delivery room.

†Includes two infants not resuscitated in delivery room.

‡Includes four stillbirths.

a logical intervention. The cost implications of intervention (bed rest) and nonintervention (neonatal intensive care) are also examined.

Material and methods

Patient data described in this report were gathered from two sources. First, all twin pregnancies cared for in Peoria for a four-year period from 1974 through 1977 were studied. (Triplets were not included, and higher multiples did not occur). Information was collected from delivery room records of the three hospitals providing obstetrical care, and was supplemented by state perinatal records and newborn intensive care records. Gestational age was determined from maternal dates for all infants not transferred to the Newborn Intensive Care Unit. Prolonged bed rest solely for twin pregnancy was not employed in this community during the study interval, except as noted in the discussion. Likewise, no screening programs for twins, such as routine sonography of all pregnant women, were being implemented at this time.

Second, all twin infants referred to the North Central Illinois Newborn Intensive Care Unit during this same four-year period were also included in this report. This Newborn Intensive Care Unit is part of a statewide perinatal program, and serves a region encompassing 23 counties in which approximately 18,000 live births occur annually in some 30 hospitals. Gestational age of infants admitted to the Newborn Intensive Care Unit was evaluated by the criteria of Dubowitz and associates[21] and was independently confirmed by one to three neonatologists. When gestation by maternal dates and Dubowitz criteria were discrepant by greater than two weeks, the Dubowitz estimate of gestation was used.

Hospital costs, unadjusted for inflation, were obtained from the business offices.

Results

Peoria twins. In the four-year period 218 pairs of twins were born in Peoria among 21,959 deliveries—an incidence of one in 101 deliveries. There were ten stillbirths and 28 neonatal deaths for neonatal and perinatal mortality rates of 6.6 per cent and 8.7 per cent, respectively. These compared to neonatal and perinatal mortality rates of 1.05 per cent and 1.89 per cent for all deliveries in Peoria during the same time, and thus twins accounted for 12 per cent of all neonatal deaths.

Table I lists the distribution of Peoria-born twins by gestational age. Forty-one per cent of Peoria twins were born before completing 37 weeks' gestation, and hence would classically be defined as premature. However, most of the risk of neonatal death was borne by infants of 34 weeks' gestation and less (Fig. 1). In fact, only two of the 28 neonates who died were born at 35 weeks' gestation or greater. The neonatal mortality rate for infants of 34 weeks' or less was 302.3 (26 per 86) while the rate for infants of 35 or greater weeks' gestation was 5.88 (2 per 340), a fiftyfold difference. Indeed, the neonatal mortality rate for infants of 35 or more weeks' gestation was actually half that of the entire population, although this difference is not statistically significant.

One hundred thirty-five Peoria twins (32 per cent)

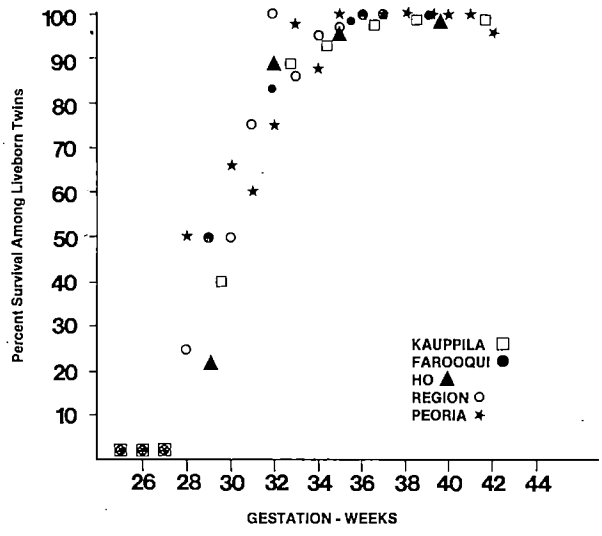


Fig. 1. Probability of survival for twins as a function of gestational age. Data of Ho and Wu,[2] Farooqui and associates,[24] and Kauppila and associates,[27] are plotted at the midpoint of the gestational age intervals they report.

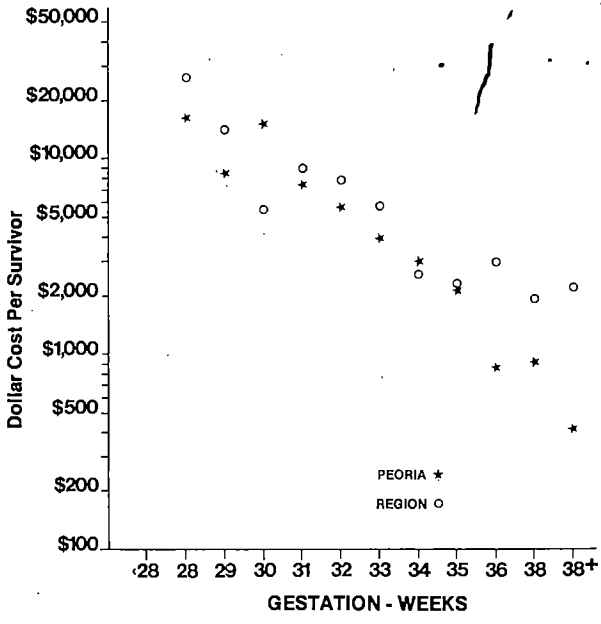


Fig. 2. Dollar cost per surviving twin as related to gestational age.

were admitted to the Newborn Intensive Care Unit and spent 2,699 days in either intensive or intermediate beds, an average of 24 days of specialized care per survivor. All Peoria-born twins of 34 weeks' gestation or less were admitted to the Neonatal Intensive Care Unit. The total intensive care bill for Peoria-born twins was approximately $440,000 or $110,000 per year. Table I also lists cost per survivor by week of gestation (total cost of care for infants of a given gestation divided by total survivors of that gestation), and Fig. 2 depicts that this cost decreases exponentially with increasing gestational age.

Regional twins. An additional 194 twin infants were referred to the Newborn Intensive Care Unit from hospitals outside Peoria. Since these infants represent only the younger and sicker members selected from a much larger, but indeterminate, population of twins, it is impossible to calculate mortality rates. Even though these data are necessarily incomplete, they are remarkably similar to the complete data gathered from Peoria babies. Thirty-six of the 37 regional neonates who died (97 per cent) were born before completion of 34 weeks' gestation. These 194 twin infants from outside Peoria required 4,458 days of intensive and intermediate care, or 28 days per survivor. Table II lists cost per survivor per week of gestation, and Fig. 2 depicts a virtually identical exponential decrease in costs with increasing gestation as was seen with the Peoria babies. The divergence noted after 35 weeks probably reflects the fact that only highly selected, very ill, infants were referred to the Intensive Care Nursery from outside Peoria.

Table III summarizes our morbidity and mortality data as related to birth before or after 34 weeks' gestation, and demonstrates the enormous risk associated with early delivery.

The magnitude of the twin problem is demonstrated by the fact that 7,157 special care days and 1.3 million dollars were expended in the care of 270 twin survivors. An average of $860 and five special care beds per day (in a nursery with an average census of 30 babies) were required to care for twins during this four-year study period.

Comment

The clinician planning bed rest for his patient pregnant with twins would probably ask at least three questions: (1) Is there a critical period when bed rest should be imposed? (2) What will it cost? and (3) Will it work? Our data suggest preliminary answers for the first two of these three questions and suggest an avenue for investigation in response to the third.

Early delivery, and its complications, is the major threat to twins.[2, 4, 5, 22–25]* These risks have most often

*Twins, of course, encounter a large number of perinatal complications.[26] Generally, however, these are fairly rare in comparison to premature delivery and its sequelae. However, late intrauterine stillbirth from presumed placental failure is of special concern. Some[13] report that this is a fairly common problem, and even advocate bed rest as a prophylactic measure late in gestation. In our series, stillbirths were rare in comparison to neonatal deaths. Hence, we do not feel that late prolonged bed rest for every twin pregnancy was warranted. Rather, it might be used in certain cases as chosen by placental function tests), hypertension, etc.

Table II. Regional twin data 1974 to 1977

Gestational age (wk.)	Admitted to NICU	Survivors	Total NICU cost $	Cost per survivor $
< 28	9	0	7,719	—
28	6	3	78,253	26,084
29	4	2	28,172	14,086
30	6	4	22,233	5,558
31	15	9	80,594	8,955
32	36	27	210,062	7,780
33	33	32	181,252	5,664
34	32	28	74,360	2,656
Subtotal ≤ 34	141	105	682,645	$\bar{X}$ = 6,501
35	17	17	38,745	2,279
36	26	26	76,062	2,925
37	3	3	5,716	1,905
≥ 38	7	6	13,158	2,193
Subtotal ≥ 35	53	52	133,681	$\bar{X}$ = 2,571
Grand total	194	157	816,326	$\bar{X}$ = 5,200

Table III. Morbidity and mortality rates of twins as related to gestational age

	Total	≤34 completed weeks' gestation	35 or more weeks' gestation	Ratio
Peoria twin neonates 1974 to 1977				
Neonatal deaths	28	26 (93)	2 (7)	13:1
Neonatal mortality rate	66	302	6	50:1
$ Cost/survivor	1,439	6,138	605	10:1
Total twin NICU experience 1974 to 1977				
Neonatal deaths				
Peoria	28	26 (93)	2 (7)	13:1
Region	37	36 (97)	1 (3)	36:1
Cost total $				
Peoria	439,393	368,259 (84)	71,134 (16)	5:1
Region	816,326	682,645 (84)	133,681 (16)	5:1
Hospital days				
Peoria	2,699	2,132 (79)	567 (21)	4:1
Region	4,458	3,566 (80)	892 (20)	4:1

Numbers in parentheses are percentages.

been expressed as a function of birth weight. However, the obstetrician who detects twin pregnancies early and considers intervention must have risk information expressed in relation to gestational age. The Peoria data, gathered during the era of newborn intensive care, suggests that completion of 34 weeks' gestation is critical, for after this degree of maturity is attained survival is nearly 100 per cent, whereas below this degree of maturity, the mortality rate is quite high. Ninety-three per cent (26 of 28) of Peoria neonates who died were born before completion of 34 weeks' gestation. Thirty-six of the 37 regional neonates who died were also born before completion of 34 weeks' gestation. Others who report their data in relation to gestational age[2, 24, 27] also find high neonatal mortality rates in twins born very early (Fig. 1).

Others[2] have described the neonatal illnesses which constitute the morbidity experienced by twins delivered at early gestations. Hospital costs are one way to quantitate this short-term illness, and Table III shows that the hospital bill per survivor born at 34 weeks' gestation or less was ten times the bill per survivor born at 35 weeks or beyond. Thus, morbidity and mortality data point to the existence of a critical period in twin gestation which spans from "viability" to completion of 34 weeks' gestation. Therefore, in answer to the first question posed earlier, if bed rest is to be employed, it is during this time, from approximately the beginning of the twenty-seventh week until the end of the thirty-fourth week, that it appears to be a logical intervention. Conversely, little can be gained by beginning or continuing routine bed rest beyond the thirty-fourth week, for morbidity and mortality rates are already quite low.

In answer to the second question, dollar costs of bed rest are readily calculable. In late 1977, a mother pregnant with twins from outside Peoria was referred to this perinatal center for bed rest. She had had a previous cesarean section, but the current pregnancy, except for the twins, was uncomplicated. She was rested in this hospital for 6 2/7 weeks, and her bill up until the time

of delivery was $715.00 per week. The cost of her delivery and postpartum recovery are not included in this calculation. Hence, $715.00 per week approximates the current cost in this hospital of prophylactic bed rest in an otherwise healthy pregnant patient, and can be used to calculate the additional expense, over and above routine costs, which would be incurred if bed rest were routinely employed. Three calculations are made, the first assuming that bed rest is completely effective in avoiding delivery before completion of 34 weeks' gestation, the second that bed rest is completely ineffective, and the third that rest is not used at all.

Completely effective bed rest. If this intervention were entirely effective in preventing delivery prior to completion of 34 weeks' gestation, and if this rest were begun early, at the beginning of the twenty-seventh week, a total of eight weeks of hospitalization per twin pregnancy would be required. In this best case, the cost of prophylactic bed rest per twin pregnancy would be $5,720 ($715 per week times 8 weeks). Since this intervention would be completely successful, there would be no intensive care costs for babies born before 34 weeks' gestation.

Completely ineffective bed rest. If bed rest were totally ineffective in prolonging twin pregnancy, but not deleterious, the same delivery pattern as has been seen over the preceding four years would prevail. Seventy-nine per cent of pregnancies would continue to deliver after 34 weeks' gestation and would have completed the entire eight-week bed rest period. The remaining 21 per cent of deliveries would continue to occur prior to 34 weeks' gestation at a mean gestational age of 31 weeks, and these mothers would have time to complete only five of the prescribed eight weeks of bed rest. Thus, the average mother would rest for 7.3 weeks and in this worst case, the bed rest cost per twin pregnancy would be $5,220 ($715 per week times 7.3 weeks). To truly reflect the cost of this ineffective intervention, the cost of the resulting newborn intensive care would have to be included. The total cost of intensive care for Peoria infants born before 35 weeks was $368,259, and there were 218 twin pregnancies. Therefore, the cost of newborn intensive care for infants of less than 35 weeks' gestation was $1,689 per twin pregnancy. Thus, the total cost of completely ineffective prophylactic bed rest would be $6,909 per twin pregnancy.

No bed rest (nonintervention). As calculated above, the current price of nonintervention is $1,689 per twin pregnancy.

Admittedly, the estimated cost of nonintervention is low, for no value was assigned to lost lives, to family suffering induced by having a child in intensive care, or to treatment and rehabilitation of potential long-term handicaps in survivors. The upper and lower estimates of the cost of bed rest are also underestimates, for no value is assigned to the resultant family disruption, to the cost of a housekeeper or other family care arrangements, or to the cost of appropriate diagnostic procedures to detect twin pregnancies. In neither case are allowances made for physician's fees.

Even though these calculations severely underestimate true costs, they do point out that pursuing either a policy of nonintervention or intervention will be expensive. One obvious way to lower costs would be to rest in some nursing home type of setting. Certainly one should be able to find a place to rest for less than $715 per week. Some women may even rest at home. Another way to lower costs would be to employ bed rest in selected high-risk cases only.[6, 28] For instance, primigravidas pregnant with twins are known to be of higher risk.[28] In this regard, it is regrettable that many early screening tests used to detect risk pregnancies[29–31] have specifically eliminated or not clearly separated out twins.

Unfortunately, even today it is still impossible to give a valid answer to the question "will bed rest work?" There are several reasons for our ignorance concerning this intervention. First, the early diagnosis of twin pregnancies has historically been a problem.[1] However, when a community makes a concerted effort with ultrasound to diagnose twins early, there can be much improvement.[32] Hormonal screening may be of additional help[32, 33] although further clarification is needed.[34, 35] Also, real-time ultrasound has enormous potential in the early diagnosis of twin pregnancies. Thus, the traditional problem of early diagnosis is solvable, although the technology available today requires wider application.

Second, a great part of the confusion concerning the efficacy of bed rest in twin pregnancy is due to the erratic way in which bed rest has formerly been used. Waiting until 36 weeks to start bed rest or continuing bed rest as late as possible[3, 17, 18] is imposing this presumed prophylactic measure far too late, well after the period of greatest risk. Similarly, beginning bed rest at 30 or 32 weeks' gestation, as is commonly practiced,[3, 15, 36–38] is again starting too late, for a large portion of the morbidity and mortality due to premature delivery occurs in infants born before this period. Not surprisingly, when bed rest is imposed at inappropriate times, evaluation of efficacy is difficult.

Third, all reports on the efficacy of bed rest are retrospective reviews and generally do not eliminate patient selection bias [i.e., a patient whose uterus was larger would be more likely to be diagnosed as a twin

pregnancy at a given gestational age, and hence rested. If larger twins resulted, was it because of the bed rest or because they were bigger to begin with? Similarly, "low-risk women" (i.e. more affluent, more health conscious) would be more likely to heed the bed rest advice. If larger twins resulted, was it because of the bed rest, or of the inherent characteristics of the mother?][1] More recent reviews on this subject still do not clarify this issue.[3, 12–16, 28]

Answering the question of the efficacy of bed rest is becoming increasingly important. Already in the reported English literature, a minimum of 88 women years of bed rest has been expended on healthy mothers solely to prolong their twin pregnancies, and still its efficacy is unproved (references available upon request). Certainly, the unreported world experience is far greater. As new technology facilitates early diagnosis of twin pregnancy, more women will undoubtedly be rested in an uncontrolled and erratic fashion, even though this intervention is of unproved benefit. Also, as more perinatal programs are implemented in the United States, and more maternal and child health funds become available,[39] these limited funds could be squandered on unproved interventions in twin pregnancies.

Hence, it becomes essential that this perinatal intervention be well evaluated at the present time. Certainly there is precedent in the United States for prospective controlled evaluation of perinatal interventions.[40] Further, there is vast experience in perinatal medicine with unfavorable results that arise from widespread application of so-called "logical" but unproved perinatal interventions. Hence, a prospective controlled trial of prolonged bed rest to improve the outcome of twin pregnancy is in order. In this study, bed rest should be applied so as to coincide with the critical period of early delivery, i.e., 27 to 34 weeks. An important end point in planning and evaluating this trial should be the prolongation of twin pregnancies beyond 34 weeks' gestation in women who rest.

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The value of diagnostic ultrasound as a screening test for intrauterine growth retardation: Comparison of nine parameters

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In an attempt to devise a screening method for the detection of unsuspected IUGR, a battery of ultrasonic measurements of the fetus were performed in a series of 255 patients at approximately 32, 34, and 36 weeks. The results obtained from the 16 growth-retarded and the 239 normally grown babies were evaluated. While no single measurement was found to discriminate the two groups, a simple combination of crown-rump length times area of trunk allowed us to identify an at-risk group comprising 11 per cent of the population. The false positive and false negative results were acceptable at levels of 10 and 6 per cent, approximately. It is considered that these results would justify a larger and prospectively randomized controlled trial to assess the benefits and drawbacks of applying these measurements in a screening schedule. (AM. J. OBSTET. GYNECOL. 134:30, 1979.)

THE COMPLICATIONS associated with intrauterine growth retardation (IUGR) are well known. However, the recognition of this problem before birth in an average obstetric population is less than satisfactory. In 1975, at the Queen Mother's Hospital in Glasgow, only 38 per cent of babies with birth weights below Lubchenco's tenth percentile[1] were recognized during the antenatal period. To achieve even this low detection rate almost five times as many pregnancies were monitored for anticipated or suspected growth retardation. Similar unsatisfactory results have been reported by Tejani, Mann, and Weiss[2] and Campbell.[3]

Among the diagnostic aids used in the antenatal monitoring of potentially growth retarded fetuses, diagnostic ultrasound has been shown to be of value in making a positive diagnosis. A number of authors have described their results, either by using serial ultrasonic measurements of the fetal biparietal diameter (BPD) to detect abnormal growth patterns or by a single measurement, to estimate weight and to screen for IUGR.[3-11] While serial cephalometry frequently permits identification of a growth-retarded fetus, this technique is impractical logistically for screening the total obstetric population, where the incidence of IUGR is approximately 5 per cent. The use of a single BPD measurement is equally unsatisfactory as a screening test as its sensitivity is only in the region of 50 per cent.[7-9]

A number of other measurements have been studied, including diameters and circumferences of the trunk,[10-17] hourly fetal urine production rates (HFUPR),[18] and total intrauterine volume (TIUV).[19] Trunk measurements alone have not been shown to reliably separate growth-retarded from normal pregnancies, although in combination with head measurements and used in form of a ratio reasonable separation has been achieved at or near term.[3, 20, 23] A low HFUPR would appear to identify well a growth-retarded fetus, but in the clinical setting the technique is impractical for routine use. Gohari, Berkowitz, and Hobbins[19] in their study of TIUV reported values below the first standard deviation line of their nomo-

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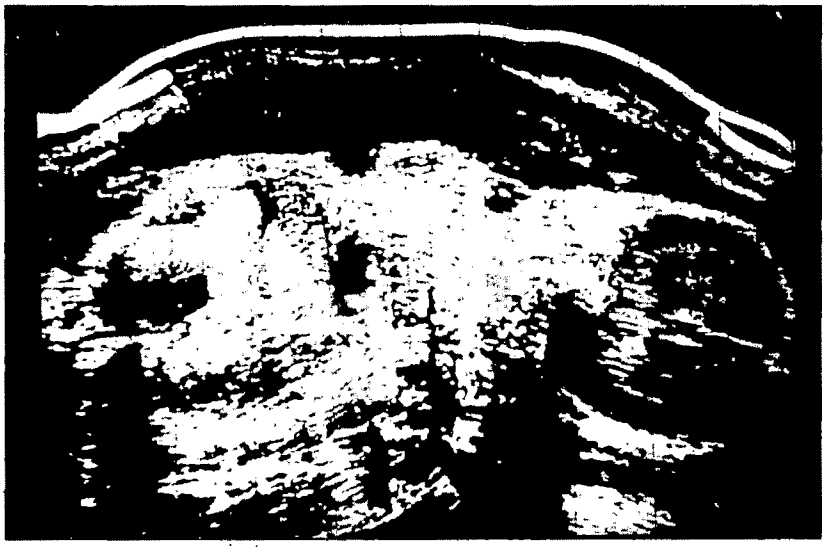


Fig. 1. Crown-rump length, 32 weeks' gestation.

gram in all 28 of the 96 "at risk" pregnancies studied which resulted in the birth of a growth-retarded fetus. There were, however, 15 of the remaining 68 normal cases in the range of −1 to −1.5 standard deviations. The authors considered that the technique was a relatively simple one and that in practice the TIUV was a good predictor of IUGR.

In designing this study, we concentrated entirely on measurements of the fetus, this being the ultimate "object" of interest. It was the aim of the study to identify which measurement or combination of measurements would best discriminate the growth-retarded from the normally grown fetus, and to determine at which gestational age the smallest number of false positive and false negative results would be incurred.

Patients and methods

A total of 255 women were selected for the study, the only criterion for admission being reliable dating of the pregnancy. The age of the pregnancy was assessed by accurate documentation of a normal menstrual cycle and last menstrual period, confirmed by an early bimanual examination of the uterus and, in over 50 per cent of patients, by an ultrasonic examination before 20 weeks.

Three ultrasonic examinations at approximately 32, 34, and 36 weeks were performed and on each occasion nine measurements were made (Table I). The equipment used was a Nuclear Enterprise Diasonograph, NE 4102, with a 2.5 MHz transducer.

A slightly modified version of Campbell's[21] combined B− and A−scan method of cephalometry was employed for the BPD measurements, with the electronic calipers calibrated to an assumed tissue velocity of 1,600 M. per second. All other measurements were performed by direct measurement from Polaroid photographs of the appropriate sections recorded on a storage oscilloscope (assumed tissue velocity of 1,540 M. per second), and corrected to life size. A standard map measurer was used for the circumference measurements and a HAF planimeter No. 315 for the area measurements.

Table I. Nine fetal parameters

Biparietal diameter (BPD)
Occipitofrontal diameter (OFD)
Head circumference (HC)
Head area (HA)
Anteroposterior trunk diameter (APTD)
Transverse trunk diameter (TTD)
Trunk circumference (TC)
Trunk area (TA)
Crown-rump length (CRL)

The crown-rump length (CRL) was measured from a section which showed both the fetal bladder and the midline of the fetal head (Fig. 1). Measurements of the occipitofrontal diameter (OFD), the circumference (HC), and the area (HA) of the fetal head were taken from elliptical sections which showed a midline echo and a short double echo one third of the way along the midline (Fig. 2).[20] The trunk measurements were obtained from a transverse section of the upper abdomen of the fetus at the level of the umbilical vein (Fig. 3). Apart from the BPD measurement, which was immediately available, the remainder of the measurements were performed without knowledge of the pre-



Fig. 2. Skull section, 32 weeks' gestation.

vious history or eventual outcome of the pregnancy.

At delivery, a diagnosis of growth retardation was made by reference to the tenth centile line on Lubchenco's weight for gestation nomogram.[1] (In the Queen Mother's Hospital only five per cent of the babies have weights at birth which fall below this line.) The gestational ages of the infants were confirmed by pediatric assessment.

All patient information, including clinical and measurement data and outcome, was then subjected to computer analysis.

Single measurements. Sixteen of the 255 babies (6.3 per cent) were found to be growth retarded[1] at delivery. For the purpose of this study, each of the three sets of measurements was used in compiling the results.

Nomograms comprising the ninetieth, fiftieth, and tenth centile lines, covering the period of study (31 to 37 weeks), were constructed from all of the measurement data for each of the nine individual parameters. The distribution of the measurements obtained from the fetuses with IUGR at delivery was then evaluated.

In this study no single parameter reliably separated the normal from the growth-retarded fetuses. With the tenth centile lines used as the dividing point, the false negative results (i.e., the percentage of results from growth-retarded fetuses found to be lying above the line) for BPD, TA, and CRL were 56, 29, and 60 per cent, respectively (Figs. 4, 5 and 6). Similar results were obtained for the other head and trunk measurements.

Combination of two measurements. The results obtained by combining two of the parameters in various ways were next examined. The best combination was found to be the product of TA and CRL (Fig. 7), with an over-all false negative rate of 33 per cent. While this rate is higher than that achieved with the "trunk area" alone, perusal of the graphs (Figs. 5 and 7) reveals that with the TA times CRL combination there were fewer false results, both negative and positive, after 235 days (33+ weeks), all but two being found in the earlier weeks. The false positive rate (the percentage of results from normally grown fetuses lying below the tenth centile line) remained fairly constant throughout the period at just under 6 per cent. In absolute figures there were 38 results below the tenth centile line after 33½ weeks, of which 14 (45 per cent) were derived from growth-retarded fetuses. These 38 data points constituted 11 per cent of all results during this period. This combination proved superior to either TTD × CRL, or TC × CRL.

Combinations providing ratios of head to trunk measurements were also examined. Of these the best was the ratio of the respective areas with a false negative rate of almost 50 per cent and an even dispersion of false results throughout the period of study.

Multiple measurements. A number of more complex computations involving three or more individual measurements were performed. The formulation giving the best separation of normal and growth-retarded fetuses was one in which HA × BPD was plotted against TA × (CRL-BPD). When individual graphs were compiled for each week of the study period (32 to 37 weeks) and the data analyzed, a very low rate of false negative results (1/45) was found (Table II), together with a rate of false positive results which fell to a reasonable level (<5 per cent) from 34 weeks onwards. The discriminatory lines for each week are shown in Fig. 8. A value falling below the appropriate line would indicate that the fetus is likely to be growth retarded.

Comment

In view of the poor antenatal detection rate of IUGR by clinical methods and the fact that such babies are at greater risk of perinatal death, neonatal morbidity, and long-term physical and mental handicap than normally grown babies, a reliable screening test would be extremely useful. To be practical, however, such a screening test should be simple, acceptable to the patient and her physician, and cost effective. It should also have a high degree of sensitivity with a low incidence of false results.

In this study a battery of fetal measurements have been evaluated both singly and in various combinations. While no single measurement was reliable in the context of a screening test, the simple combination of TA × CRL was found to separate the results from the normal and growth-retarded pregnancies after 33+ weeks with a low incidence of false negative and false

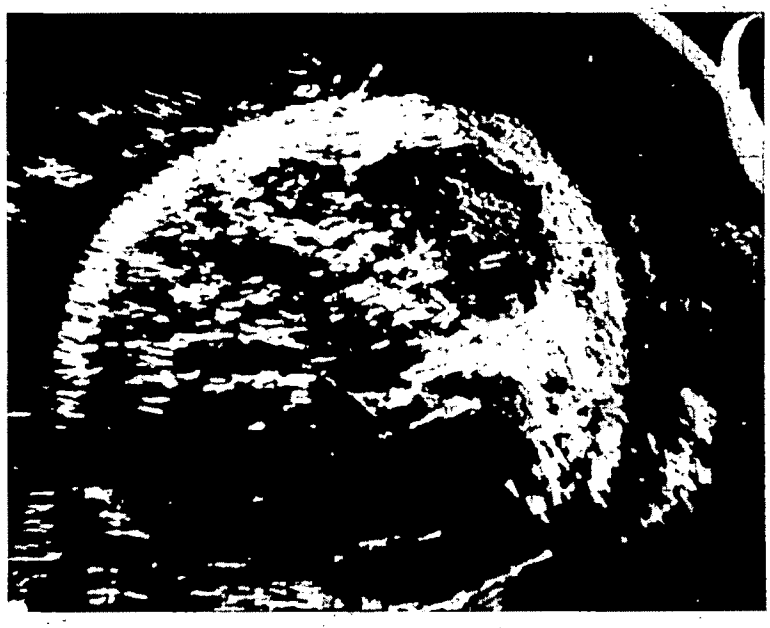


Fig. 3. Trunk section, 32 weeks' gestation.

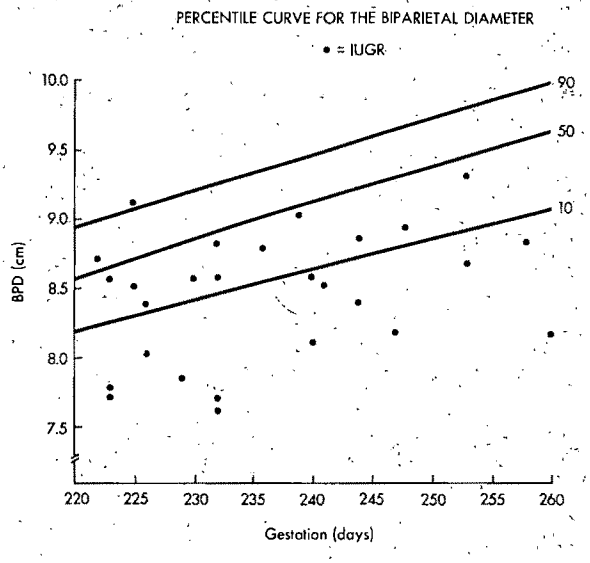


Fig. 4. Percentile curve for the biparietal diameter. Distribution of the results from fetuses born with growth retardation.

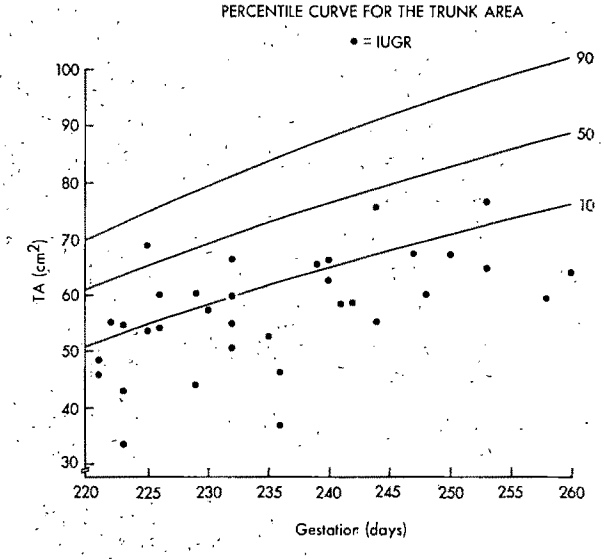


Fig. 5. Percentile curve for the trunk area. Distribution of the results from fetuses born with growth retardation.

positive findings. In numerical terms, this combination allowed us to identify an "at risk" group, which comprised 11 per cent of the population with almost one half (45 per cent) of this 11 per cent being true positive results. In addition it missed only 10 per cent of the results from growth-retarded fetuses, with an over-all false positive rate of approximately 6 per cent.

With the more complex system where a value related to head volume (head area × BPD) is plotted against a value related to trunk volume [trunk area × (CRL − BPD)], slightly lower rates of false results were achieved. While this system is inherently less attractive because of the greater number of measurements involved, it has certain merit in that it incorporates a ratio of head "size" to body "size," a parameter which is often abnormal in growth-retarded fetuses. Furthermore, the measurements more closely approximate to the fetal volume and therefore fetal weight.

While we appreciate that the numbers involved in this study are small, these findings are encouraging, with a pick-up rate of growth-retarded fetuses much in excess of that achieved by routine clinical means, and

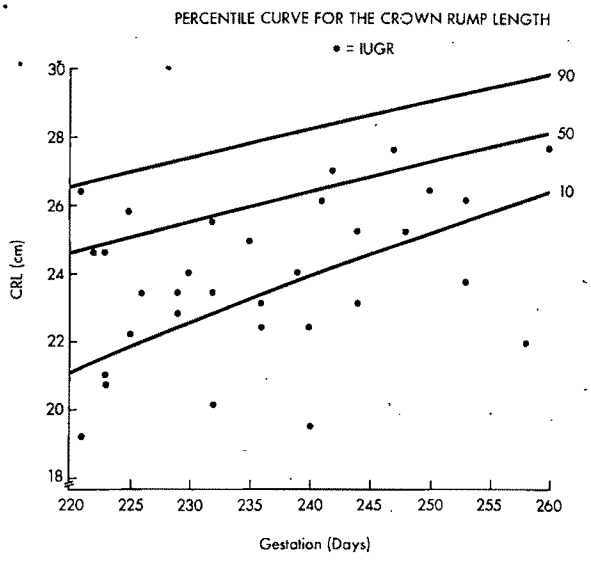


Fig. 6. Percentile curve for the crown-rump length. Distribution of the results from fetuses born with growth retardation.

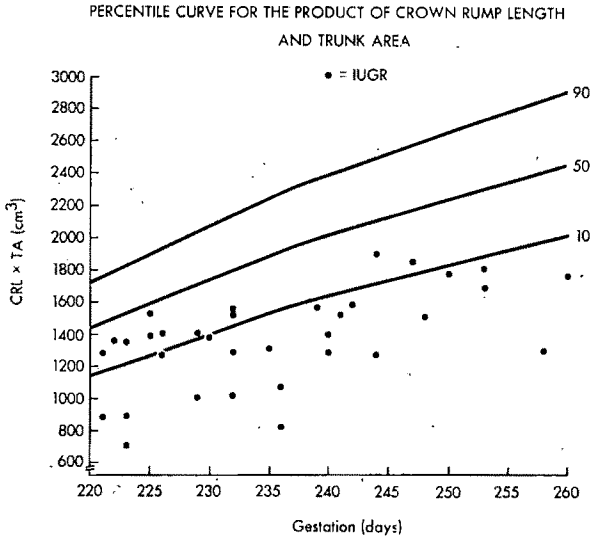


Fig. 7. Percentile curve for the product of crown-rump length and trunk area. Distribution of the results from fetuses born with growth retardation.

with a rate of false results which would be tolerable logistically.

In our experience and with the equipment used in this study, the sections required for the complete set of measurements may be obtained with little difficulty and on average require less than 10 minutes per patient. However, the map measurer and planimeter are awkward to use and are potentially inaccurate, especially when photographs of scan converter images are used.[22] To overcome these problems, Fleming and associates[22] designed an electronic measuring device which allows measurements to be made directly from the gray-scale display. With this instrument, area and perimeter measurements can be obtained rapidly and with a high degree of accuracy. As a result, it is considered that a large-scale screening program is now practicable. Before advocating the more widespread application of such a program, however, answers should be sought to the following questions. (1) Would the investment in resources and manpower be justified in terms of improved perinatal mortality and morbidity rates? (2) Would iatrogenic morbidity be increased as a result of inappropriate decisions being taken in the false positive and false negative groups? We plan to approach these problems by conducting a prospective randomized controlled trial.

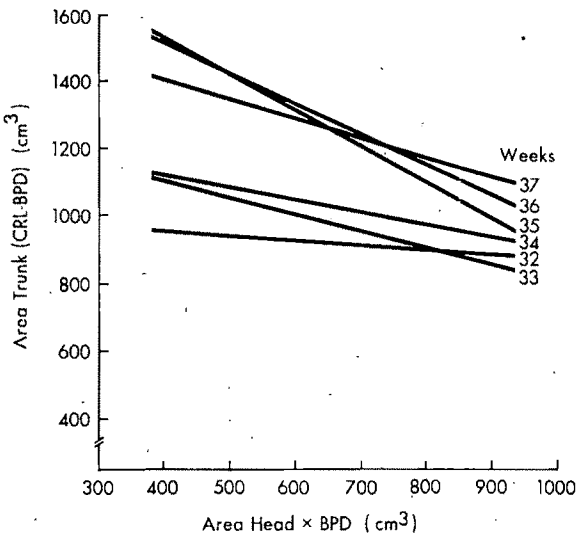


Fig. 8. Discriminatory lines from 32 to 37 weeks' gestation in the identification of fetuses born with growth retardation. HA × BPD is plotted against TA × (CRL − BPD).

Table II. False positive and false negative results in the identification of fetuses born with growth retardation*

Week of gestation	No. of results			
	Normal	Growth retarded	False positive	False negative
32	104	9	21 (20%)	—
33	100	10	11 (11%)	—
34	112	10	5 (4%)	1
35	108	7	5 (5%)	—
36	91	5	1 (1%)	—
37	45	4	—	—

*HA × BPD is plotted against TA × (CRL-BPD).

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Fetal heart rate acceleration in labor: Excellent prognostic indicator

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This study explores the significance of fetal heart rate acceleration in labor. Fetal heart rate accelerations were studied in 1,677 monitored laboring patients. Fetal outcome was analyzed according to perinatal mortality rate, Apgar scores, and incidence of late deceleration. The presence of accelerations of the fetal heart rate during labor proved to be an excellent indicator of subsequent good fetal outcome. (AM. J. OBSTET. GYNECOL. 134:36, 1979.)

SINCE the early sixties the role of electronic monitoring in the management of labor has assumed increasing importance. The initial three basic patterns described by Caldeyro-Barcia and colleagues[1] and Hon[2] have been refined so that now a great number of patterns can be identified and closely associated with variants in fetal condition. In this study an extension of the work of Rochard in France and Schifrin in this country[3] was carried from the antepartum period into labor. They have originally described the usefulness of antepartum nonstress testing with good subsequent fetal outcome. In this study we have attempted to correlate fetal heart rate acceleration in labor with a similar prognosis.

Materials and methods

During the 12 months from January 1, 1976, to December 31, 1976, 2,265 infants were delivered at DePaul Hospital, which is one of the teaching hospitals of the Eastern Virginia Medical School. Of these patients, 1,677 (74 per cent) were monitored electronically by means of standard Corometrics 111B monitors.* Internal monitoring by means of a scalp electrode was utilized in 1,276 patients. Intrauterine catheter was used in 848 patients. The remainder were monitored externally with Toco transducers and external ultrasound technique. Since the staff and residents have an agreed policy of total monitoring, the only reasons for not monitoring patients were precipitous labor, lack of availability of a monitor, or elective cesarean section.

The patients were drawn from both the private and clinic segments of the obstetric population in the ratio of 65 per cent private to 35 per cent clinic. It was, therefore, felt that this represented a cross-section of an average obstetric population.

Classification of recognized fetal heart rate and uterine contractility changes follow the standard classification of Hon.[2] An acceleration was defined as an increase of fetal heart rate of 15 beats per minute above the normal baseline occurring with a contraction. Three accelerations occurring in a 15 minute period were necessary for inclusion in the acceleration category. Only uniform fetal heart rate acceleration patterns are included. Those accelerations occurring in association with decelerations or representing rebound phenomena were excluded from this study.

Results

The results of this study are detailed in Table I. The perinatal mortality rate for all patients delivered at DePaul Hospital in 1976 was 18.6 per thousand. The perinatal mortality rate for that group of monitored patients was 14.9 per thousand. Fetal heart rate accelerations were present in 953 of those patients monitored (56.8 per cent) while no accelerations were observed in 724 patients (43.2 per cent). It is important to note the marked decrease in the perinatal mortality

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Table I. Perinatal data

Category	*Number percentage*	*Late decelerations*	*5 Minute Apgar < 7*	*Perinatal mortality rate*
Total deliveries	2,265/100%	—	57/2.5%	18.6/1,000 (42 deaths)
Monitored	1,677/74%	87/5.2%	34/2.0%	14.9/1,000 (24 deaths)
Nonmonitored	588/26%	—	23/3.9%	27.2/1,000 (18 deaths)
Accelerations present	953/56.8%	11/1.15%*	8/0.84%*	4.2/1,000* (4 deaths)
Accelerations absent	724/43.2%	76/10.49%*	76/10.49%*	27.5/1,000* (20 deaths)

*$P < 0.01$.

rate of those patients who exhibited fetal heart rate accelerations in labor. Only four patients showing this fetal heart rate change died, giving this group of patients the the excellent perinatal mortality rate of 4.2 per thousand. These four deaths were due to beta streptococcus pneumonia in a term infant, intracranial hemorrhage in a 37 week gestation infant delivered by midforceps, and respiratory distress syndrome in two preterm infants. The group of patients that did not show accelerations in labor had a much higher perinatal mortality rate of 27.5 per thousand, 20 deaths having occurred in this group. In evaluating these 20, it was found that conditions often associated with hypoxia (i.e. diabetes, postmaturity, sepsis, pre-eclampsia) were readily demonstrable in 16 patients. One may conjecture that the loss of accelerations in these infants can be related to the underlying pathophysiology of the fetal-placental unit, especially in cases where obvious causes of placental dysfunction can be demonstrated. Obvious explanations, however, are not available for all of these patients as two pre-term infants died of respiratory distress syndrome and two died from congenital anomalies.

The improved outcome of neonates who showed intrapartum fetal heart rate accelerations is likewise demonstrated by observing the incidence of low Apgar scores and late decelerations in the varied groups studied. Five-minute Apgar scores of less than 7 occurred in only eight patients (0.84 per cent) with acceleration patterns present, while 26 patients (3.9 per cent) without accelerations had 5 minute Apgar scores of less than 7. The difference in the occurrence of late decelerations between the two groups is likewise striking. Only 11 patients (1.15 per cent) with accelerations exhibited late decelerations while 76 patients (10.49 per cent) without accelerations had late decelerations (Table I).

The significance of the values of each of these three subgroups was evaluated with a chi square technique, and differences for all three groups were found to be significant to a probability factor of less than 0.01.

While no differentiation was made between vertex and nonvertex presentations when statistics were computed, breech presentations were examined separately. Of the 91 breech presentation infants delivered in this series, 76 were monitored. Only two of these failed to show accelerations in labor. There was one death among the breech deliveries. It occurred secondary to severe hypoxia in a vaginal delivery. Interestingly, accelerations were not present during labor.

Comment

Rochard and associates[3] have shown that fetal heart rate accelerations in response to fetal movement in the nonlaboring patient correlate well with fetal well-being and that this correlation can be used as a basis for a useful antepartum test. This assumption is based on the fact that fetal heart rate accelerations in response to movement are indicative of an intact and well-oxygenated central nervous system and secondary appropriate cardiac response.

The benign aspects of a reactive acceleration pattern have been amply demonstrated in every study in which this sign has been looked for. In analyzing baseline recordings of fetal heart rate and uterine activity, both Schifrin[4] and Trierweiler and colleagues[5] have shown that the presence of increased accelerations virtually precludes the development of late decelerations in the subsequent stress of induced contractions. While the absence of accelerations has been shown to carry a much more ominous prognosis, it is not as accurate a predictor of poor outcome as accelerations with movement are of good outcome.[6] It would appear that our data substantiate the premise that a fetus with an intact neurocardiac system as demonstrated by accelerations in labor has sufficient reserve in terms of levels of oxygenation and placental reserve to well tolerate the rigors of labor. Our data suggest that, just as they do in

the antepartum period, fetal heart accelerations lend reassurance in the intrapartum situation that the fetus who is healthy and shows the proper response to the stress of contractions, as demonstrated by accelerations, has an excellent likelihood of tolerating labor and delivery without difficulty. While the absence of fetal heart rate accelerations is not as accurate a predictor of fetal distress, this lack of acceleration can, nonetheless, alert the obstetrician to be especially judicious in the use of procedures which may stress the fetus further. If accelerations are present, one can be confidently reassured, often very early in the labor period, that the chances of good fetal outcome are excellent. However, if accelerations are not present, one should observe the patient even more closely, being careful to assure adequate hydration, avoiding the supine position, using analgesia and anesthesia with care, and being alert for signs of fetal distress.

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Demonstration of immunoreactive somatostatin-like substance in villi and decidua in early pregnancy

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With the use of the radioimmunoassay for growth hormone–releasing inhibiting factor (GIF), it was found that measurable amounts of GIF-like substance existed in the chorionic villi and decidua of pregnant women. The indirect immunofluorescent method revealed that the higher intensity of GIF-like immunofluorescence was presented in cytotrophoblasts rather than in syncytiotrophoblasts of the villi and in stromal cells of the decidua. (AM. J. OBSTET. GYNECOL. 134:39, 1979.)

SINCE ARIMURA and associates[1] reported the method for the measurement of somatostatin (growth hormone–releasing inhibiting factor [GIF]) by radioimmunoassay (RIA), the existence of GIF-like substance has been demonstrated in various organs and tissues by both the RIA and immunohistochemical methods. Dubois, Paulin, and Assan[2] found, after using the immunohistochemical method, that the GIF-like substance localized in the descrete cells of the Langerhans islets of the pancreas in addition to the hypothalamus. Such a wide distribution of GIF-like substance may lead to the concept that GIF is not a systemic but a local hormone. In the placenta, little is known as to whether or not the release of placental hormones is under the control of some local hormones. However, it may be reasonable to assume that some unknown local hormones participate in the regulation of known hormonal activities during pregnancy. In this study, we attempted to demonstrate the existence of GIF-like substance in villous and decidual cells in early gestation with the RIA for GIF and the immunofluorescent technique of Barry, Dubois, and Carette.[3]

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Material and methods

The antiserum of GIF was prepared by immunizing rabbits with synthetic somatostatin conjugated to bovine serum albumin (BSA) with glutaraldehyde. The ratio of somatostatin and BSA was 1:4. The complex antigen obtained was emulsified with complete Freund's adjuvant. The emulsion was injected as multiple intradermal injections on the shaven backs of the rabbits. This antiserum was tested by the RIA and the precipitation method, by agar. The antiserum of human chorionic gonadotropin (HCG) was offered from Mochida

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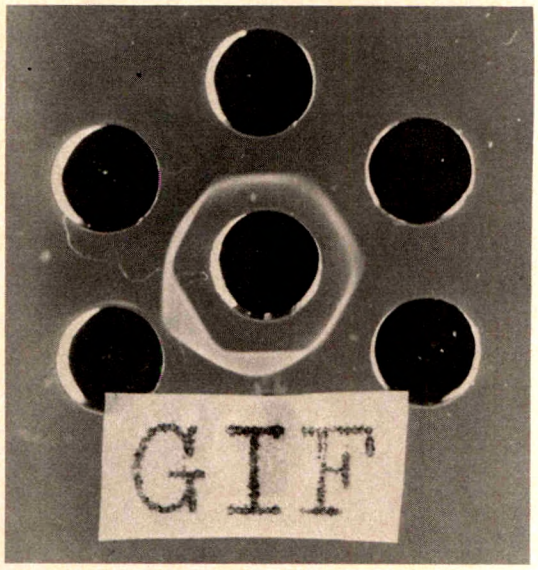


Fig. 1. Microimmunodiffusion pattern of GIF. A precipitin band is seen between the antigen *(outside)* and antibody wells *(central)*.

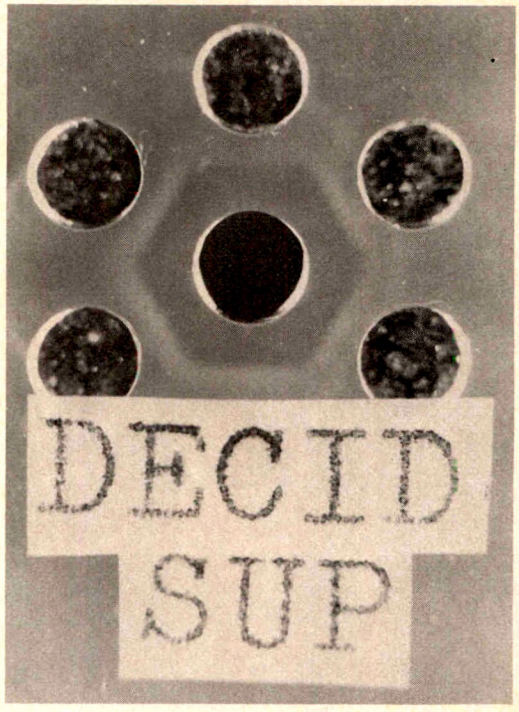


Fig. 2. Microimmunodiffusion pattern of the decidual extract. A precipitin band is seen between the wells of extract *(outside)* and of antibody *(central)*.

Pharmaceutical Company (Tokyo, Japan). A total of 0.10 ml. of the anti-hCG serum at a dilution ratio of 1:1,000,000 could neutralize 1.0 mI.U. of hCG.

Immunodiffusion test. The micro–multiple diffusion test was performed by the method of Crowle.[4] The slide glass was coated with agar* dissolved in 0.15M sodium chloride and 0.05M phosphate buffer (pH 7.2) containing 0.1 per cent sodium azide, and solidified. The wells were punched in the agar layer with a capillary glass tube and charged with the reactant and antibody.

Radioiodination and RIA of GIF. One microgram of (Tyr^8)-GIF, 100 ng. per 2 μl of lactoperoxidase,† and 10 μl of 0.05M ammonium acetate buffer, pH 5.0 (A.A.B.), were added to 500 μCi of ^{125}I-sodium.‡ The reaction was started by adding 2 μl (204 ng.) of hydrogen peroxide (diluted 1:5,000 with deionized water). After 5 minutes the reaction was terminated by diluting with 1 ml. of 0.002M ice-cold A.A.B., pH 4.6. The reaction mixture was immediately applied on a carboxymethylcellulose column (1 by 8 cm.) equilibrated with 0.002M A.A.B. and then with 0.2M A.A.B. at 4° C. The tubes containing ^{125}I-(Tyr^8)-GIF were stored at −20° C. until used.

All dilutions were made with standard diluent consisting of 0.1 per cent gelatin, 0.025M ethylenediaminetetraacetate 0.15M sodium chloride, and 0.01M phosphate buffer, pH 7.5 (GPBS). A total of 100 μl of a known amount of GIF or sample solution was added to a mixture of 200 μl of GPBS and 100 μl of anti-GIF serum with a final dilution of 1:2,500. This concentration of anti-serum was sufficient to bind 25 to 40 per cent of ^{125}I-(Tyr^8)-GIF in the absence of unlabeled GIF. Then 100 μl of ^{125}I-(Tyr^8)-GIF was added. The tubes were incubated for 24 hours at 4° C. After incubation, 500 μl of dextran-coated charcoal solution was added, and the tubes were incubated for an additional 15 minutes at 4° C. Finally, the tubes were centrifuged at 3,000 r.p.m. for 30 minutes and the supernatant was decanted. The precipitate was counted with a well-type counter. All samples were assayed in duplicate. The detailed procedure for GIF-RIA will appear elsewhere.*

Extraction procedure of GIF-like substance from villi and decidua. Human villous and decidual tissues were obtained from cases of spontaneous and legal abortion at 5 to 12 gestational weeks. The material was collected in a tubes containing 0.5 ml. of Trasylol (10,000 K.I.U. Bayer, West Germany), homogenized with 5 ml. of 2N acetic acid at 0° C., and centrifuged at

*Noble agar, Difco Labs., Detroit, Michigan.
†Sigma Chemical Co., St. Louis, Missouri.
‡New England Nuclear, Boston, Massachusetts.

*Sawano, S., et al.: In preparation.

Table I. The concentration of immunoreactive GIF-like substance in villi and decidua

	Concentration of GIF-like substance (pg./0.1 Gm. dry weight)			
	Villi		*Decidua*	
Gestation (wk.)	*Normal pregnancy*	*Abortion*	*Normal pregnancy*	*Abortion*
6	23.5		20.8	24.5
6	17.4		22.0	
7	N.D.*	N.D.		22.0
8	25.3	21.7	20.6	38.2
8		20.3	21.2	
9	19.8	N.D.	22.5	
10				25.0
11	17.2	N.D.		10.6
11		21.0		
12		17.5		100.0

*N.D. = Not detectable.

3,000 r.p.m. for 30 minutes. The supernatant was lyophilized. The extract was dissolved with GPBS when assayed.

Immunofluorescence. The chorionic villi and decidua were obtained from pregnant women at 6 to 8 gestational weeks by legal abortion. These tissues were immediately washed with ice-cold 0.15M saline in order to remove blood. After fixation for 2 to 3 days in Bouin's-Holland's fluid, the tissues were carefully washed with 0.1M phosphate buffer, pH 7.8, dehydrated by ethanol, and embeded in paraffin. The tissues were sliced at 10 μm thickness with a microtome and the sections were treated with the indirect immunofluorescence technique on a slide glass. Namely, the sections were treated with rabbit anti-GIF serum (dilution ratio 1:20) for 50 min. at room temperature, and immersed in anti-IgG with fluorescein isothiocyanate (1:5 dilution) for 50 min. Then the preparations were washed three times with 0.1M phosphate buffer for 5 min. and finally fixed with 0.5 per cent aqueous gelatin. The other preparations were treated with either GIF-absorbed anti-GIF serum or normal rabbit serum as the control tests. The reaction was studied with an Olympus fluorescence microscope.*

Results

Immunodiffusion test. The precipitin band formed a circular fusion between the wells of GIF and of anti-GIF serum. According to Crowle,[4] this coalescence of the proximal band tips signified a reaction of identity (Fig. 1). This pattern of GIF reaction similarly was seen in decidual immunodiffusion as shown in Fig. 2.

*Olympus Optical Ltd., Tokyo, Japan

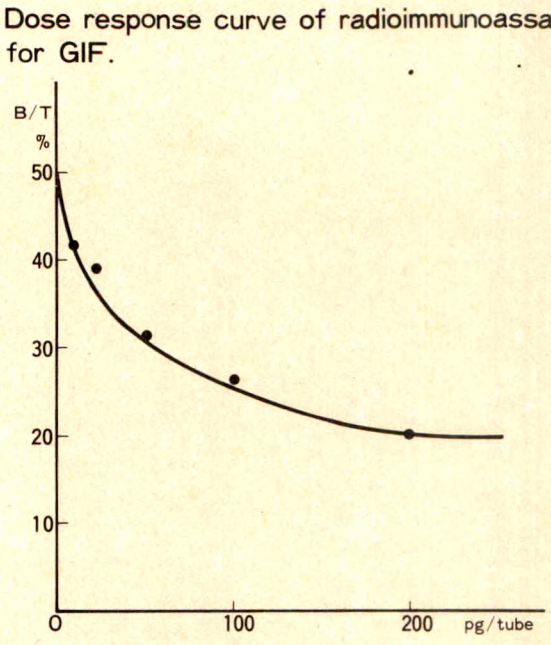


Fig. 3. Standard curve for the radioimmunoassay of GIF. The intra-assay and interassay variances were 6.1 and 12.4 per cent, respectively.

RIA of GIF. The standard curve of GIF was shown in Fig. 3. As little as 3.9 pg. per tube of synthetic GIF was detected in this assay system. No significant competition was observed between synthetic GIF and other peptide hormones tested (oxytocin, vasopressin, thyroid stimulating hormone–releasing hormone (TRH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactin, growth hormone (GH), adrenocorticotropic hormone (ACTH), and hCG, except luteinizing hormone releasing factor (LHRF) which slightly cross-reacted with anti-GIF at the dose of 10 μg (Fig. 4). The displacement curves of the extracts from both villi and decidua were parallel with that of standard GIF (Fig. 4).

As shown in Table I, GIF-like immunoreactivity was detected in the villi in five of six normal pregnant women and in four of seven women who had abortions. Such immunoreactivity was found in all decidua obtained from both normal women and those who had abortions.

Immunofluorescence. The immunoreactive cells were located along the syncytial layer of chorionic villi, but the intensity of immunofluorescence in the cytotrophoblast was higher than that in the syncytiotrophoblast. The immunofluorescence was not visible in the stromal cells of the villi (Fig. 5). The immunoreactivity was not visible in chorionic villi treated with normal rabbit serum (Fig. 6).

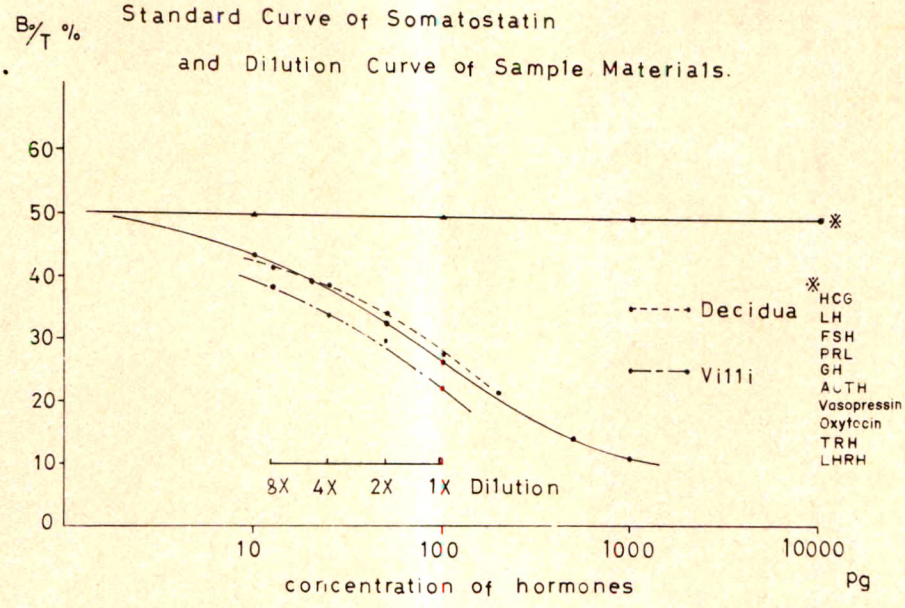


Fig. 4. Cross-reaction of peptide hormones and villous and decidual extracts.

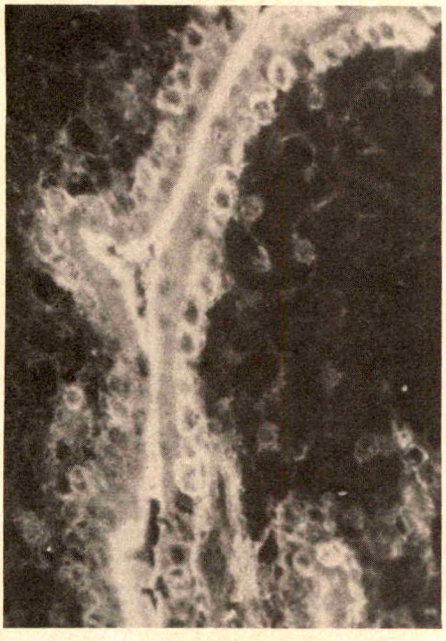


Fig. 5. GIF immunoreactive cells are present in cytotrophoblasts rather than in syncytiotrophoblasts (7 weeks' gestation).

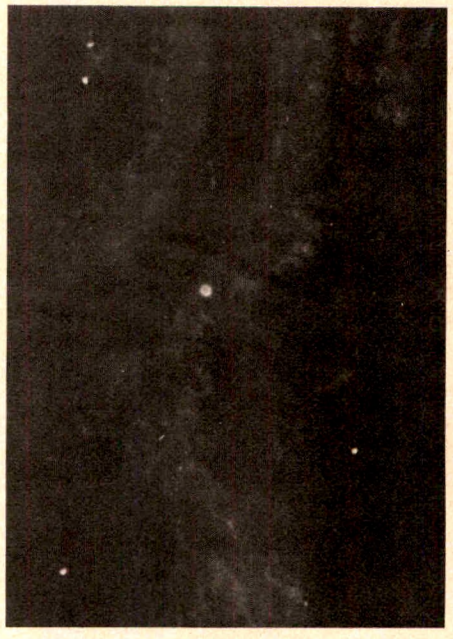


Fig. 6. Villous tissue of 7 weeks' gestation after an application of normal rabbit serum. No immunoreactive cells are seen.

On the other hand, the decidual stromal cells also reacted to the immunofluorescence, while such a reactivity was not observed in the epithelium of the endometrial glands (Fig. 7). The immunofluorescence was not seen when the tissues were treated with normal rabbit serum (Fig. 8). These findings differed from those of immunofluorescence with hCG; the hCG immunoreactive cells were located in the syncytiotrophoblasts rather than in the cytotrophoblasts, and immunofluorescence was not found in the control specimen treated with normal rabbit serum (Figs. 9 and 10).

Comment

The existence of immunoreactive GIF has been demonstrated in the hypothalamus and brain of the human fetus between 10 and 20 weeks' gestation.[5] In



Fig. 7. GIF immunoreactive cells seen in the decidual stroma of 7 weeks' gestation.



Fig. 9. hCG-immunoreactive cells seen in both the cytotrophoblasts and syncytiotrophoblasts of 7 weeks' gestation.

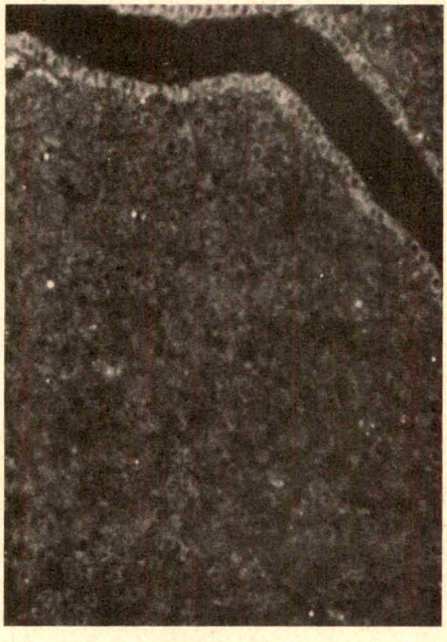


Fig. 8. Decidual tissue of 7 weeks' gestation after an application of normal rabbit serum. No immunoreactive cells are seen.



Fig. 10. Villous tissue treated with normal rabbit serum, immunofluorescent hCG-immunoreactive cells not seen.

addition, it has been shown that immunoreactive GIF is widely distributed in the pancreas and stomach as well as in the central nervous system.[6–9] On the other hand, immunoreactive GIF had never been demonstrated in the cells of chorionic villi and decidua. It is well known that chorionic villi produce some peptide hormones and steroids. Recently, Riddick and Kusmik.[10] reported that the amount of prolactin released from the decidua far exceeded a decrease in the tissue content of prolactin during incubation.

The releasing mechanism of the various peptide hormones from the chorionic villi and decidua is of

interest. In the rat hypothalamus, it was observed that a quantity of immunoreactive GIF is present in dendrites or axons of the nerve cells. However, a fluorescent reaction with anti-GIF was recognized neither in nerve fibers nor in nerve endings throughout the pancreas.[2, 6] In the present study, it was found with the use of RIA that GIF-like substance exists in the villi and decidua. Furthermore, the localization of GIF-like substance in the cells was demonstrated on the basis of the immunohistochemical method. On the basis of these findings, it is possible that GIF-like substance is present in the decidua and placenta. Whether or not villous and decidual GIF-like substances participate in the control of chorionic peptide or steroid secretion during gestation remains unknown.

Further investigation is necessary to elucidate the site of GIF synthesis.

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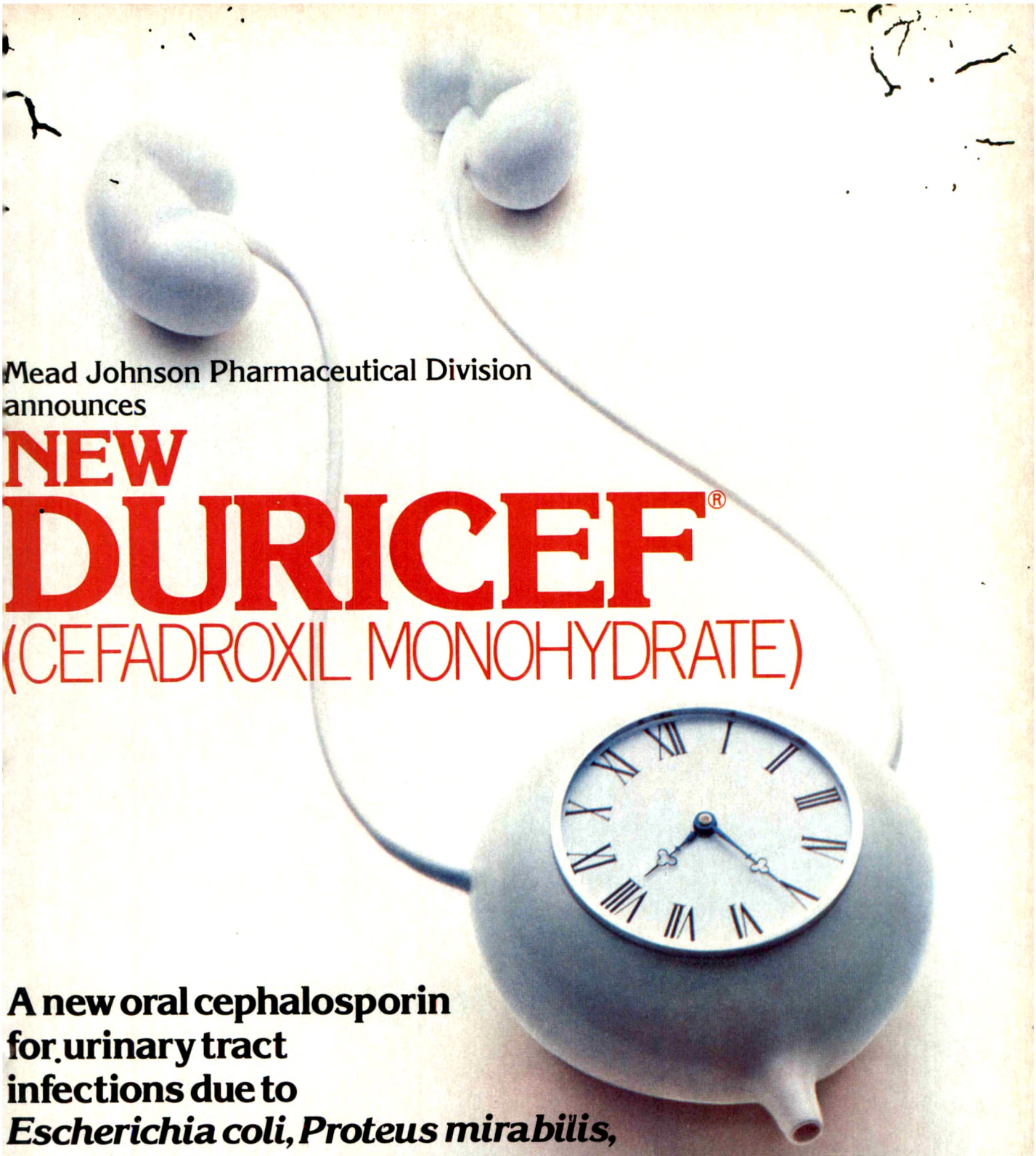
Seventh Annual Conference on Perinatal Medicine: Perinatal Genetics

The Seventh Annual Conference on Perinatal Medicine: Perinatal Genetics will be held May 17 and 18, 1979, at Callaway Gardens, Pine Mountain, Georgia.

For information contact: Micki L. Souma, M.D., or Louis I. Levy, M.D., Perinatology, The Medical Center, P. O. Box 951, Columbus, Georgia 31902.

Mead Johnson Pharmaceutical Division
announces

NEW DURICEF®
(CEFADROXIL MONOHYDRATE)

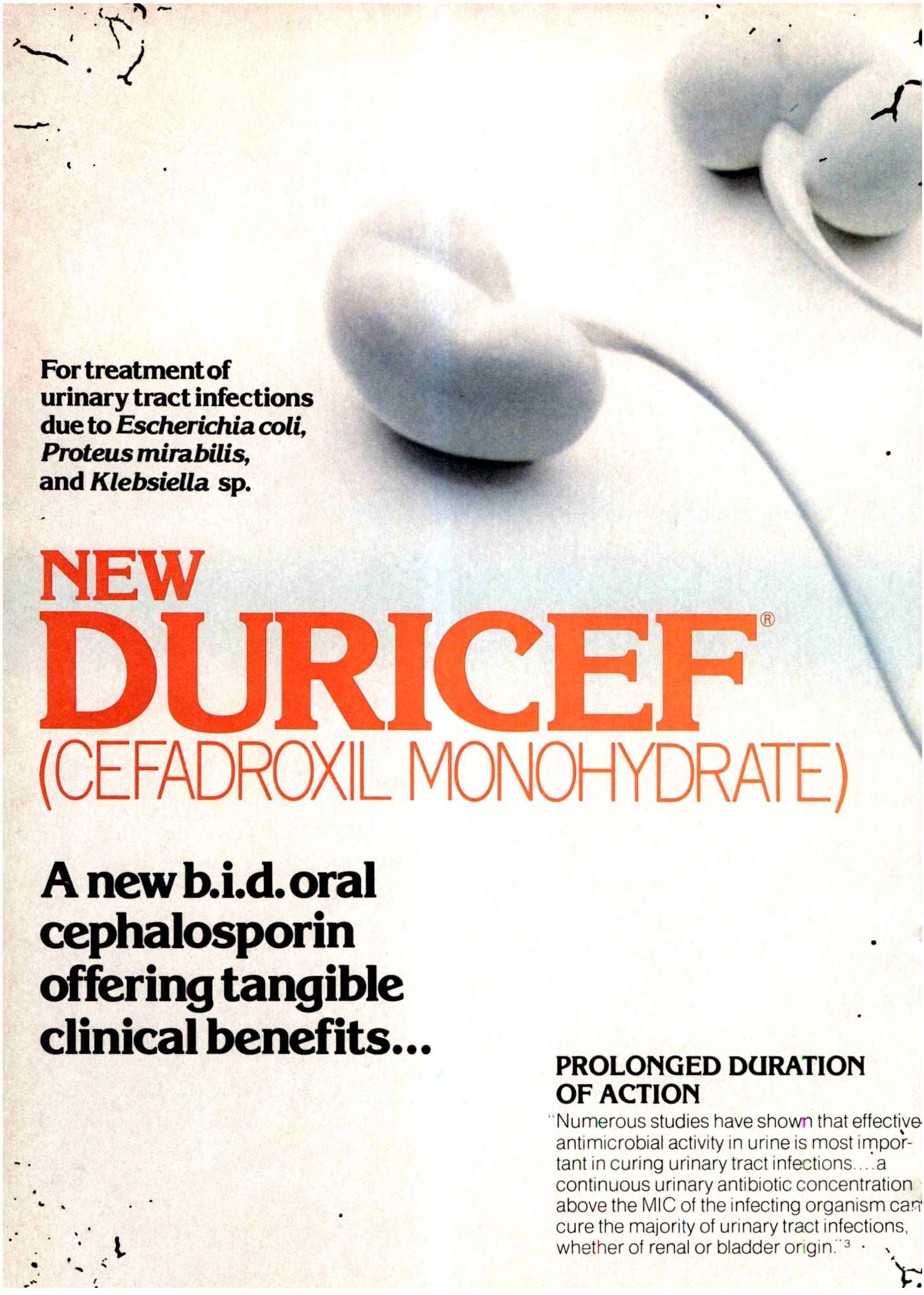


A new oral cephalosporin for urinary tract infections due to *Escherichia coli, Proteus mirabilis,* and *Klebsiella* sp. distinguished by sustained, higher urine levels

"Numerous human pharmacological studies have now clearly established that the outstanding metabolic characteristic of cefadroxil, which differentiates it from other presently marketed cephalosporins such as cephalexin and cephradine, is its prolonged duration of action."[1]

"...for cephalosporins, a longer half-life might be more useful than higher peak levels."[2]

For complete prescribing information, see last page of this advertisement.



For treatment of urinary tract infections due to *Escherichia coli*, *Proteus mirabilis*, and *Klebsiella* sp.

NEW DURICEF®
(CEFADROXIL MONOHYDRATE)

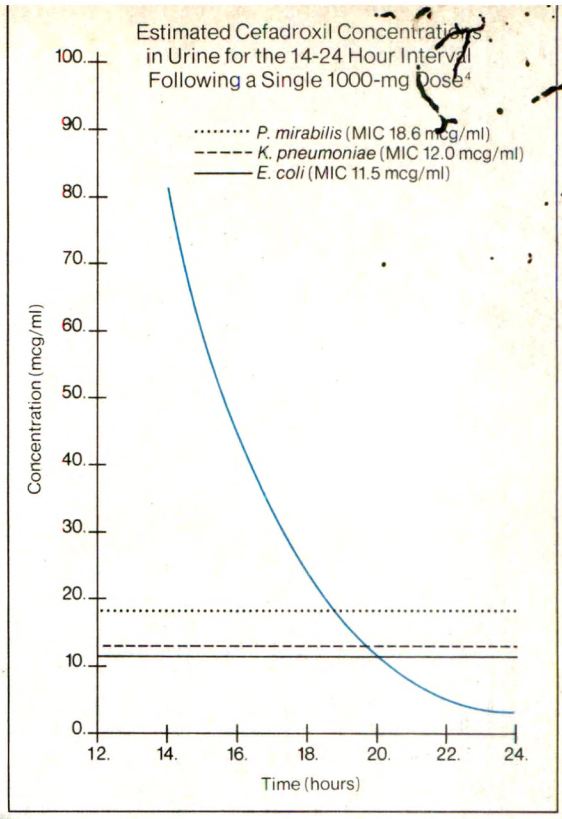
A new b.i.d. oral cephalosporin offering tangible clinical benefits...

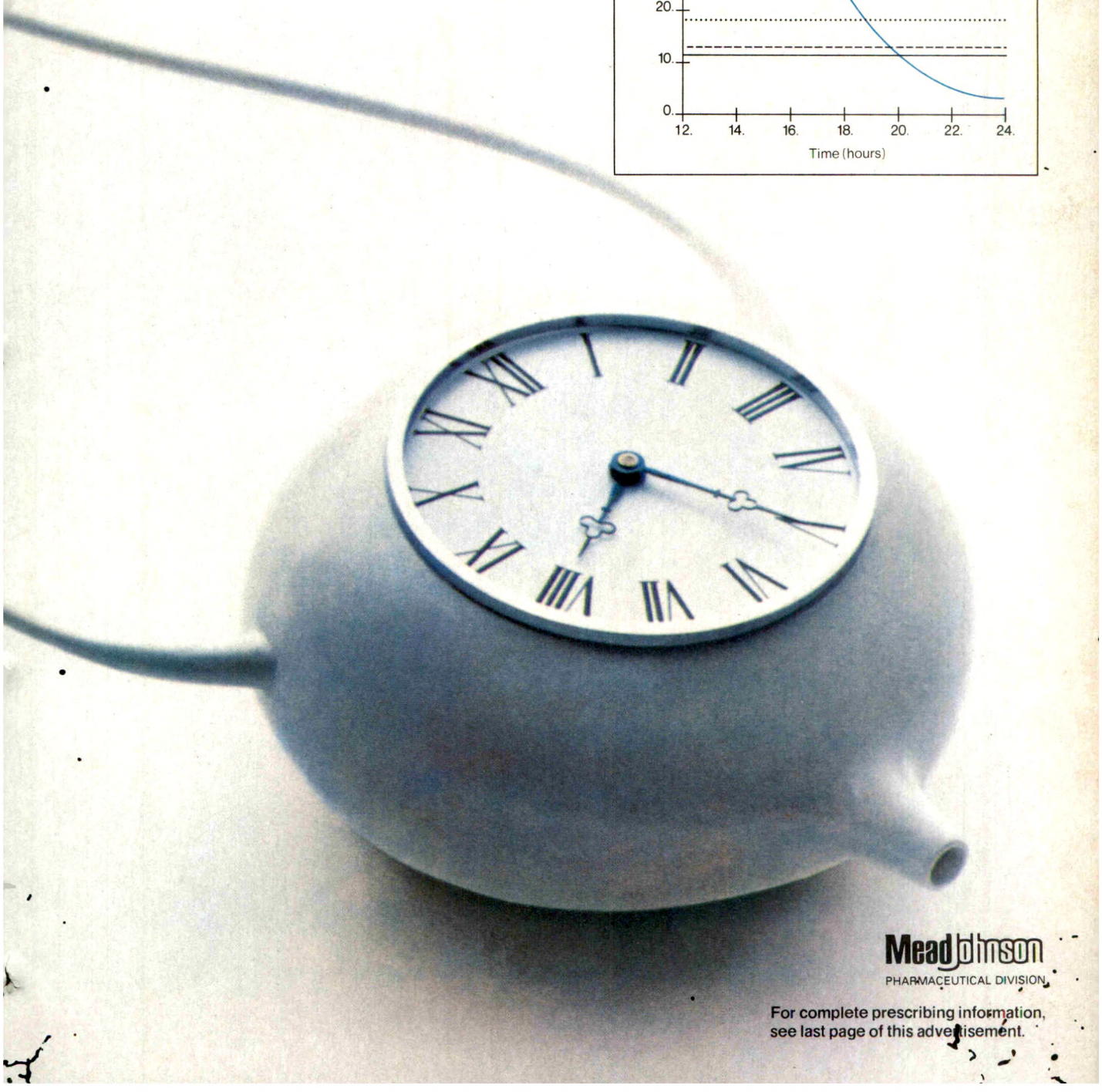
PROLONGED DURATION OF ACTION

"Numerous studies have shown that effective antimicrobial activity in urine is most important in curing urinary tract infections....a continuous urinary antibiotic concentration above the MIC of the infecting organism can cure the majority of urinary tract infections, whether of renal or bladder origin."[3]

SUSTAINED HIGHER URINE LEVELS

- Cefadroxil concentration in urine is maintained well above the MICs for all typical urinary pathogens for 12 hours and, in most instances, for 18 hours.[3]
- After single equivalent doses, the antibiotic concentration in urine is three times higher for cefadroxil at 6 to 12 hours than for cephalexin.[3]
- The prolonged duration of action is due to a more gradual urinary excretion rate compared to cephalexin and cephradine.[1,3]
- Twenty-four hours after ingestion, approximately 93% of cefadroxil is recovered in the urine.[3]





Mead Johnson
PHARMACEUTICAL DIVISION

For complete prescribing information, see last page of this advertisement.

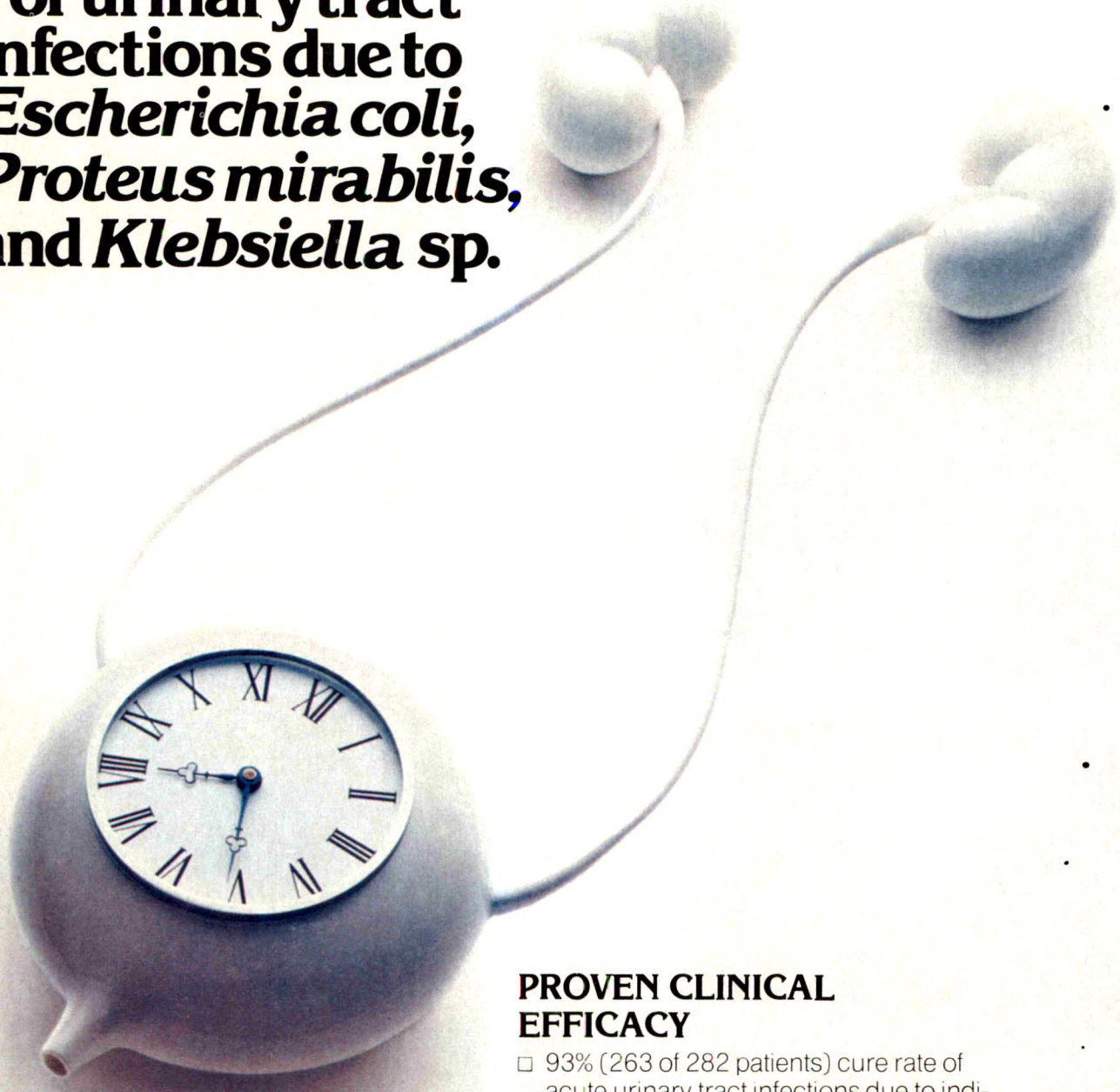
NEW

CAPSULES, 500 mg.

DURICEF®

(CEFADROXIL MONOHYDRATE)

For urinary tract infections due to *Escherichia coli*, *Proteus mirabilis*, and *Klebsiella* sp.



PROVEN CLINICAL EFFICACY

- 93% (263 of 282 patients) cure rate of acute urinary tract infections due to indicated organisms in the patients treated with cefadroxil (two 500-mg. capsules b.i.d.) in numerous multicenter studies.[5]

HIGH DEGREE OF SAFETY

- Laboratory parameters in more than 175 studies in 15 countries have failed to reveal any drug-related changes regarded as clinically significant.[4]
- In none of these studies was there any tendency for cefadroxil to accumulate in the serum nor has nephrotoxicity been reported.[4]
- DURICEF can be used in patients with renal insufficiency at reduced dosages (see full prescribing information).
- There is evidence of partial cross-allergenicity between the penicillins and the cephalosporins.
- The most frequent adverse reaction has been nausea...rarely severe enough to warrant cessation of therapy. Administration with food decreases the chances of nausea occurring and does not affect absorption.

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B.I.D. CONVENIENCE AND COMPATIBILITY WITH FOOD

B.I.D. CONVENIENCE

Sustained high urine levels in comparison with other oral cephalosporins justify a simple two-capsule b.i.d. regimen in urinary tract infections.

COMPATIBILITY WITH FOOD

Concomitant administration of DURICEF with food does not affect its rate or extent of absorption. This may be helpful in diminishing potential gastrointestinal complaints occasionally associated with oral cephalosporin therapy.

ENHANCED DOSAGE COMPLIANCE

The convenient regimen of DURICEF—two capsules b.i.d., at breakfast and dinner—improves the chances for patient compliance and increases the likelihood of patients completing therapy as prescribed.



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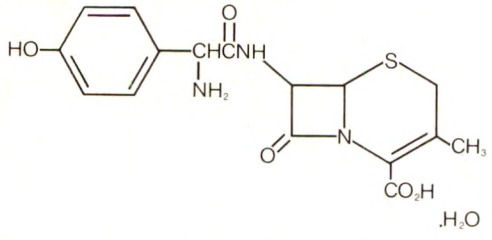
For complete prescribing information, see following page.

DURICEF®
(CEFADROXIL MONOHYDRATE)



A new oral cephalosporin offering tangible clinical benefits... plus b.i.d. convenience

DESCRIPTION: DURICEF® (cefadroxil monohydrate) is a semisynthetic cephalosporin antibiotic intended for oral administration. It is a white to yellowish-white crystalline powder. It is soluble in water and it is acid-stable. It is chemically designated as 7-[[D-2-amino-2-(4-hydroxyphenyl)acetyl]amino]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid monohydrate. It has the following structural formula:



Clinical Pharmacology—DURICEF (cefadroxil monohydrate) is rapidly absorbed after oral administration. Following single doses of 500 and 1000 mg., average peak serum concentrations were approximately 16 and 28 mcg./ml., respectively. Measurable levels were present 12 hours after administration. Over 90 percent of the drug is excreted unchanged in the urine within eight hours. Peak urine concentrations are approximately 1800 mcg./ml. during the period following a single 500 mg. oral dose. Increases in dosage generally produce a proportionate increase in DURICEF urinary concentration. The urine antibiotic concentration was maintained well above the MIC of all typical urinary pathogens for 12 hours and, in most instances, for 18 hours.

MICROBIOLOGY: *In vitro* tests demonstrate that the cephalosporins are bactericidal because of their inhibition of cell-wall synthesis. DURICEF is active against the following organisms *in vitro*:

Escherichia coli — *Klebsiella species*
Proteus mirabilis

Note—Most strains of *Enterococci (Streptococcus faecalis* and *S. faecium)* are resistant to DURICEF. It is not active against most strains of *Enterobacter species, P. morganii,* and *P. vulgaris.* It has no activity against *Pseudomonas* or *Herella species.*

Disc Susceptibility Tests—Quantitative methods that require measurement of zone diameters give the most precise estimates of antibiotic susceptibility. One recommended procedure (CFR Section 460.1) uses cephalosporin class disc for testing susceptibility; interpretations correlate zone diameters of this disc test with MIC values for DURICEF. With this procedure, a report from the laboratory of "resistant" indicates that the infecting organism is not likely to respond to therapy. A report of "intermediate susceptibility" suggests that the organism would be susceptible if the infection is confined to the urinary tract, as DURICEF produces high antibiotic levels in the urine.

INDICATIONS: DURICEF (cefadroxil monohydrate) is indicated for the treatment of urinary tract infections caused by *E. coli, P. mirabilis,* and *Klebsiella species.*

Note—Culture and susceptibility tests should be initiated prior to and during therapy. Renal function studies should be performed when indicated.

CONTRAINDICATION: DURICEF (cefadroxil monohydrate) is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNING: IN PENICILLIN-ALLERGIC PATIENTS, CEPHALOSPORIN ANTIBIOTICS SHOULD BE USED WITH GREAT CAUTION. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES OF PATIENTS WHO HAVE HAD REACTIONS TO BOTH DRUGS (INCLUDING FATAL ANAPHYLAXIS AFTER PARENTERAL USE).

Any patient who has demonstrated a history of some form of allergy, particularly to drugs, should receive antibiotics cautiously and then only when absolutely necessary. No exception should be made with regard to DURICEF (cefadroxil monohydrate).

PRECAUTIONS: Patients should be followed carefully so that any side-effects or unusual manifestations of drug idiosyncrasy may be detected. If a hypersensitivity reaction occurs, the drug should be discontinued and the patient treated with the usual agents (e.g., epinephrine or other pressor amines, antihistamines, or corticosteroids).

DURICEF (cefadroxil monohydrate) should be used with caution in the presence of markedly impaired renal function (creatinine clearance rate of less than 50 ml/min/1.73 M^2). (See Dosage and Administration.) In patients with known or suspected renal impairment, careful clinical observation and appropriate laboratory studies should be made prior to and during therapy.

Prolonged use of DURICEF may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Positive direct Coombs tests have been reported during treatment with the cephalosporin antibiotics. In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs test may be due to the drug.

USAGE IN PREGNANCY: Although no teratogenic or anti-fertility effects were seen in reproductive studies in mice and rats receiving dosages greater than the normal human dose, the safety of this drug for use in human pregnancy has not been established. The benefits of the drug in pregnant women should be weighed against a possible risk to the fetus.

ADVERSE REACTIONS: Gastrointestinal—The most frequent side-effect has been nausea. It was infrequently severe enough to warrant cessation of therapy. Administration with food decreases nausea and does not decrease absorption. Diarrhea and dysuria have also occurred.

Hypersensitivity—Allergies (in the form of rash, urticaria, and angioedema) have been observed. These reactions usually subsided upon discontinuation of the drug.

Other reactions have included genital pruritus, genital moniliasis, vaginitis, and moderate transient neutropenia.

DOSAGE AND ADMINISTRATION: DURICEF (cefadroxil monohydrate) is acid stable and may be administered orally without regard to meals. Administration with food may be helpful in diminishing potential gastrointestinal complaints occasionally associated with oral cephalosporin therapy.

Adults—The usual adult dose is one g. (two 500 mg. capsules) two times per day for patients with normal renal function. In patients with renal impairment, the dosage of cefadroxil should be adjusted according to creatinine clearance rates to prevent drug accumulation. The following schedule is suggested. In adults, the initial dose is 1000 mg. of DURICEF (cefadroxil monohydrate) and the maintenance dose (based on the creatinine clearance rate [ml/min/1.73M^2]) is 500 mg. at the time intervals listed below.

Creatinine Clearances	Dosage Interval
0-10 ml/min	36 hours
10-25 ml/min	24 hours
25-50 ml/min	12 hours

Patients with creatinine clearance rates over 50 ml/min may be treated as if they were patients having normal renal function.

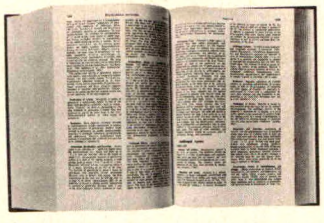
Children—Dosage and safety have not yet been established in children.

HOW SUPPLIED: DURICEF® (cefadroxil monohydrate) capsules 500 mg. for oral administration in an opaque maroon cap and opaque white body No. 0 hard gelatin capsule. On each half capsule printed in black is "MJ" and "500." Available in bottles of 24 capsules (NDC 0087-0784-41) and 100 capsules (NDC 0087-0784-42). U.S. Patent Re—29,164

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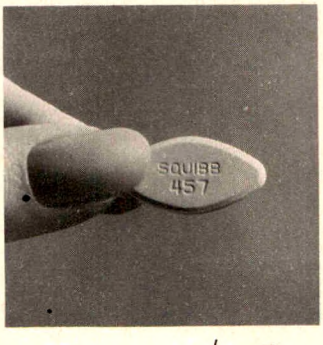
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Good reasons to look at MYCOSTATIN® Vaginal Tablets (Nystatin Vaginal Tablets U.S.P.) again



Little or no resistance

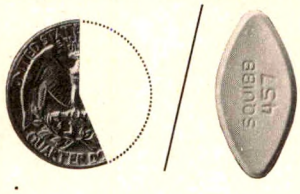
"Repeated subculture of *Candida albicans* in increasing concentrations of nystatin results in little or no development of resistance..."[1] No occurrence of *in vivo* resistance as a general rule.



Virtually nontoxic and nonsensitizing

The manual application option

The fact that a vaginal tablet can be inserted *without* an applicator offers an important option when such a method is deemed advisable by the physician.



Economy

Your patients can save substantially compared to the cost of Miconazole Nitrate Cream or Clotrimazole Vaginal Tablets.*

Mycostatin® Vaginal Tablets

Nystatin Vaginal Tablets U.S.P.

[1]Goodman & Gilman, *The Pharmacological Basis of Therapeutics*, 5th Ed, 1975, p. 1236

*Based on manufacturers' published prices to retailers.

See following page for brief summary.

MYCOSTATIN® Vaginal Tablets
Nystatin Vaginal Tablets U.S.P.

MYCOSTATIN® VAGINAL TABLETS
Nystatin Vaginal Tablets USP

DESCRIPTION: Mycostatin Vaginal Tablets (Nystatin Vaginal Tablets USP) are provided as diamond-shaped compressed tablets containing 100,000 units of nystatin dispersed in lactose with ethyl cellulose, stearic acid, and starch.

INDICATIONS AND USAGE: This product is effective for the local treatment of vulvovaginal candidiasis. Confirm diagnosis by KOH smears and/or cultures prior to therapy. Rule out Trichomonas and *H. vaginalis* by appropriate laboratory methods since these pathogens do not respond to nystatin.

CONTRAINDICATIONS: Contraindicated in patients with a history of hypersensitivity to any of the components of the tablets.

PRECAUTIONS: General—Discontinue therapy if sensitization or irritation is reported during use.

Laboratory Tests—Repeat microbiological studies to confirm diagnosis and rule out other pathogens before instituting another course of antimycotic therapy if there is a lack of response to nystatin vaginal tablets.

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GYNECOLOGY

Galactorrhea and pituitary tumors in postpill and non-postpill secondary amenorrhea

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One hundred sixty-seven women with secondary amenorrhea were observed from six months to four years. In 66 patients, the amenorrhea followed the discontinuation of oral contraceptives (postpill) while in the remaining 101 the amenorrhea was not temporally pill related (non-postpill). Galactorrhea was present in 43 (65%) of those with postpill amenorrhea and in 32 (32%) of those with non-postpill amenorrhea ($p < 0.001$). Tomography of the sella turcica was performed in the 75 women with galactorrhea and in the 35 without galactorrhea who did not have withdrawal uterine bleeding following progesterone administration and who had low or normal serum follicle-stimulating hormone levels (hypothalamic-pituitary failure). Forty of the 75 patients with amenorrhea and galactorrhea had radiographic evidence of a pituitary tumor whereas only eight of 35 patients with hypothalamic-pituitary failure without galactorrhea had an abnormal sella turcica ($p < 0.01$). The incidence of radiographic abnormalities in those with galactorrhea was similar in both the postpill and non-postpill groups. (AM. J. OBSTET. GYNECOL. 134:45, 1979.)

THE MOST POPULAR contraceptive method in the United States is the use of oral contraceptive steroids.[1] These steroids are used by approximately 12 million women.[2] The incidence of amenorrhea of more than six months after discontinuation of oral contraceptives is estimated to be between 0.2 and 0.8%.[3, 4]

Recently, pituitary tumors have been reported to occur in patients with postpill amenorrhea with or without galactorrhea.[5] It is not known whether these tumors are induced by oral contraceptives or whether the steroid-associated withdrawal bleeding and inhibition of lactation mask the major symptoms of pituitary tumors.

This study was undertaken to ascertain if women who develop postpill amenorrhea differ from women with secondary amenorrhea *not* following oral contraceptive use.

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Table I. Secondary amenorrhea study group

	Postpill	*Non-postpill*
N (total-167)	66	101
Age (yr.)	16-36	16-39
Prior menses:		
Oligomenorrhea	30 (45%)	37 (37%)
Regular	36 (55%)	64 (63%)
Parous	18 (27%)	32 (32%)
Amenorrhea (mo.):		
Range	6-132	6-216
Median	24	35
Amenorrhea without galactorrhea	23 (35%)	69 (68%)
Amenorrhea and galactorrhea	43 (65%)	32 (32%)

Materials and methods

The records of all Endocrine-Infertility Clinic patients presenting with secondary amenorrhea between July, 1974, and June, 1977, were reviewed. Criteria for inclusion in the study group were: (1) secondary amenorrhea of at least six months' duration, (2) no prior therapy with injectable steroidal contraceptives, (3) age less than 40 years, (4) no pregnancy within the previous 12 months, and (5) no breast-feeding for at least two years. Patients with elevated serum levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) were diagnosed as having ovarian failure and none of these patients was included.[6] A total of 167 patients between 16 and 39 years of age met these criteria (Table I).

Sixty-six patients had no spontaneous menses following the discontinuation of oral contraceptives. These patients were placed in the postpill category. In the other 101 patients there was no such temporal relation between the amenorrhea and oral contraceptive use. These patients were placed in the non-postpill category. At the initial visit, following a history and complete physical examination, the patients were further classified by the presence or absence of galactorrhea into four groups: (1) postpill amenorrhea (PPA), 23 patients; (2) postpill amenorrhea and galactorrhea (PPAG), 43 patients; (3) non-postpill amenorrhea (NPPA), 69 patients; and (4) non-postpill amenorrhea and galactorrhea (NPPAG), 32 patients. The women with galactorrhea had bilateral breast secretions which were either spontaneous or elicited by gentle pressure. The estrogen status of all patients without galactorrhea was determined by intramuscular administration of progesterone in oil.[6] Serum levels of FSH and LH were measured in all patients. Serum prolactin (PRL) levels were measured only in the 75 patients with galactorrhea. All assays were performed by previously described radioimmunoassay techniques.[7, 8] In this laboratory, the 95% confidence limits of hormone values during the follicular phase of normal ovulatory cycles are 3.2 to 9.0 mI.U./ml for FSH, 5 to 25 mI.U./ml for LH, and 9 to 20 ng./ml for PRL.

Hypocycloidal tomograms of the sella turcica were obtained in 110 patients—the 75 patients with galactorrhea as well as the 35 patients without galactorrhea who did not have withdrawal bleeding following progesterone administration and who had low or normal serum FSH levels (hypothalamic-pituitary failure).[6] The latter two categories were selected for sellar tomography since in a prior study abnormal pituitary fossa roentgenograms were reported to occur only in patients with these characteristics.[6] Polytomograms were interpreted by one neuroradiologist without knowledge of the patient's history or laboratory data. The tomograms were considered abnormal if there was inferolateral asymmetry of sella floor exceeding 2 mm. with associated erosion of the lamina dura.[9] Roentgenography was performed annually in all patients whose symptoms persisted.

Results

Postpill patients. Of the 66 patients in this category, 30 (45%) had oligomenorrhea prior to oral contraceptive use and 18 (27%) were parous (Table I). The length of amenorrhea varied between six and 132 months with a median of 24 months. The duration of oral contraceptive use ranged from one to 132 months with a median of 29 months. The mean age at the time oral contraceptive use was begun was 21 years with a range of 14 to 32 years.

Of these patients, 23 (35%) did not have galactorrhea and were characterized as having PPA (Table I). The other 43 (65%) had galactorrhea and were characterized as having PPAG. Of the 30 patients with prior oligomenorrhea, 19 developed PPA and 11 had PPAG.

PPA. Of the 23 patients with PPA, 13 had uterine bleeding following progesterone administration and 10 did not bleed. Of the 13 patients who had withdrawal bleeding, three had elevated LH but normal FSH levels in serum and the remaining 10 patients had normal FSH and LH concentrations. The 10 patients who did not have withdrawal bleeding had either low or normal serum LH and FSH values. Only two of the patients who failed to have withdrawal bleeding after progesterone had abnormal tomograms of the sella turcica. Initial and follow-up roentgenograms have remained normal in the other eight patients.

PPAG. Of these 43 patients, 17 had progesterone-induced withdrawal bleeding and 26 did not bleed. Serum LH and FSH levels were normal or low in the 43 patients with PPAG. Serum PRL levels were elevated (27 to 1,900 ng./ml) in 33 patients (77%).

Twenty-two patients (51%) had radiographic evidence of a pituitary tumor. Of these 22 patients, seven had withdrawal bleeding and 15 did not. Of the 33 patients with hyperprolactinemia, 20 had radiographic abnormalities.

Non-postpill patients. Of the 101 patients in this category, 37 (37%) had oligomenorrhea prior to the onset of amenorrhea and 32 (32%) were parous (Table I). At the time of referral to the clinic, these patients had been amenorrheic between six months and 18 years with a median of 35 months.

Of the 101 patients, 69 (68%) did not have galactorrhea and were classified as having NPPA (Table I). The other 32 (32%) had galactorrhea and were classified as having NPPAG. Of the 37 patients with prior oligomenorrhea, 26 had NPPA and 11 developed NPPAG.

NPPA. Of the 69 patients with NPPA, 44 had withdrawal bleeding following progesterone and 25 did not. All of these patients had normal or low serum LH and FSH levels. Tomograms of the sella turcica revealed abnormalities in six of the 25 patients who failed to respond to progesterone.

NPPAG. Of the 32 patients with NPPAG, 11 had withdrawal bleeding following intramuscular progesterone and 21 did not. All patients had normal serum levels of FSH and LH. Serum PRL levels were elevated (27.5 to 2,900 ng./ml) in 21 of these patients (66%).

Of these patients, 18 (56%) had radiographic evidence of a pituitary tumor while 14 (44%) had normal roentgenograms. Only two of the 18 patients with abnormal roentgenograms had bleeding after progesterone administration. Of the 21 patients who had elevated PRL levels, 15 had abnormal tomograms.

Radiographic abnormalities. Because the prevalence of abnormal roentgenograms in the PPAG group (51%) was similar to that in those with NPPAG group (56%), the two groups were combined and compared to those postpill and non-postpill patients without galactorrhea who had hypothalamic-pituitary failure. Of the 75 patients with amenorrhea and galactorrhea (PPAG and NPPAG), 40 (53%) had radiographic evidence of a pituitary tumor whereas only eight of the 35 patients (23%) without galactorrhea had radiographic evidence of a pituitary tumor. This difference is statistically significant ($p < 0.01$).

Comment

In this study, 45% of the patients in the postpill category had a prior history of oligomenorrhea. However, this percentage is not significantly different from the finding of previous oligomenorrhea in 36% of the patients from the non-postpill group. This suggests that a significant number of women who have oligomenorrhea may become amenorrheic at a later date irrespective of oral contraceptive use. Although it has been suggested that a causal relation exists between oligomenorrhea and the development of secondary amenorrhea following oral contraceptive treatment, the natural history of oligomenorrhea with and without contraceptive steroid use is unknown.[11] Also, the incidence of galactorrhea in both the postpill and non-postpill groups was not higher among patients who had prior oligomenorrhea. These data suggest that there may be no relation between present menstrual pattern and the subsequent occurrence of galactorrhea in those who develop amenorrhea.

The incidence of galactorrhea was significantly higher in women with postpill amenorrhea than in patients from the non-postpill group ($p < 0.001$). These data indicate a relation between oral contraceptive use and the development of galactorrhea in women who became amenorrheic after discontinuing the use of oral steroid contraceptives.

Amenorrheic women who have hypothalamic-pituitary failure and those with galactorrhea irrespective of whether or not they have progesterone withdrawal bleeding should have roentgenography of the sella turcica. This is supported by the finding of abnormal tomograms in 23% and 53%, respectively, of these two groups of patients. Amenorrheic women with galactorrhea compared with the group having hypothalamic-pituitary failure and no galactorrhea had a significantly greater incidence of abnormal sella turcica roentgenograms. Pituitary tumors were found in a high percentage of women with galactorrhea independent of estrogen status. Thus, unlike women who have only amenorrhea, all of those with galactorrhea, regardless of estrogen status, should have roentgenography of the sella turcica. This increased incidence of radiographic abnormalities was similar in both the PPAG and NPPAG groups. However, it should be noted that 65% of the women who developed amenorrhea following oral contraceptive use had galactorrhea compared with only 32% of the patients in the non-postpill category. Therefore, the difference in the proportion of radiographic abnormalities compatible with a pituitary tumor is related to the significantly greater incidence of galactorrhea; since galactorrhea is more frequent in patients with postpill amenorrhea, these patients are in a higher risk category for presence of a pituitary tumor.

The cause of the high incidence of galactorrhea and pituitary tumors observed in women with amenorrhea following termination of oral contraceptives cannot be explained at present. Because both estrogens[8, 12, 13] and

gestagens[14, 15] have been shown to stimulate PRL release, oral contraceptive steroid preparations may be causally related to the development of galactorrhea, by direct stimulation of the pituitary lactotrophs, by inhibition of the release of prolactin-inhibiting factor, or by stimulation of the growth of very small asymptomatic pituitary tumors.[16] In order to determine whether a causal relationship exists between the use of oral contraceptives and the development of pituitary tumors, it will be necessary to perform a retrospective case-control study.

The reagents used for LH, FSH, and PRL assays were supplied by the National Institute of Arthritis, Metabolism, and Digestive Diseases, Bethesda, Maryland.

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Surgical treatment of prolactin-secreting microadenomas

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Fourteen women (aged 19 to 38 years) with amenorrhea of 1 to 7 years' duration underwent transsphenoidal pituitary exploration for selective removal of potential prolactin secreting microadenomas. Preoperatively, serum prolactin levels were elevated in all (90 to 970 ng/ml), standard sella turcica x-ray films were normal, but polytomography revealed localized erosion in 12 women. Growth hormone reserve (assessed with insulin-induced hypoglycemia) was compromised in one of 13 women; cortisol responsiveness (to insulin-induced hypoglycemia) was attenuated in three of 10 women, while gonadotropin reserve (assessed with subcutaneous 100μg luteinizing hormone–releasing factor) was borderline in two of 13 women. At operation, pituitary adenomas were removed in 13 women, while a sellar diverticulum was found in the remaining woman. In the 13 women with pituitary adenoma removal, plasma prolactin levels decreased in all and reached normal levels in five women. Despite pituitary surgery, trophic hormone function (i.e., growth hormone reserve, cortisol responsiveness, thyroid-stimulating hormone, follicle-stimulating hormone, and luteinizing hormone) was preserved in most instances and perhaps improved. Adjunctive radiotherapy was utilized in two patients. With follow-up of 6 months' to 3 years' duration, cyclic menses have resumed in six and pregnancy occurred in three of seven women desiring fertility. Factors associated with successful surgical treatment of these microadenomas included: (1) tumor size (<8 mm in diameter), (2) surgical technique, and (3) the surgeon's operative experience.
(AM. J. OBSTET. GYNECOL. 134:49, 1979.)

WIDE AVAILABILITY of sophisticated radiologic techniques[1] and increasingly sensitive laboratory assays of hypothalamic pituitary hormones[2] have allowed a more frequent identification of a small prolactin-secreting adenoma (microadenoma) of the pituitary in some hyperprolactinemic-amenorrheic women. The treatment of these tumors remains controversial and various therapeutic modalities have been advocated, including surgical extirpation,[3] radiotherapy,[4] and medical therapy[5] (i. e., bromoergocryptine). The experience of the Reproductive Endocrinology Division at Duke University Medical Center with surgical therapy (transsphenoidal resection of prolactin-secreting pituitary microadenomas) over a period of 2 years (January, 1975, to June, 1977) is reported.

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Material and methods

Fourteen women (aged 19 to 38 years) with amenorrhea of 1 to 7 years' duration were thoroughly studied prior to operation. Galactorrhea was present in 10 of the women. The onset of amenorrhea (with or without galactorrhea) was spontaneous in six of the patients, coincident with the discontinuation of oral contraceptives in six patients, post partum in one patient, and as a primary occurrence in one patient. Complete physical examination and formal visual field determinations were normal in all of the patients except for one who was congenitally blind. The relevant clinical aspects and laboratory data are summarized in Table I.

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Table I. Prolactin-secreting microadenomas: Baseline laboratory data

Case No.	*Age of patient (yr.)*	*Duration of amenorrhea (yr.)*	*Galactorrhea*	*Prolactin (ng/ml)*	*FSH (mIU/ml)*	*LH (mIU/ml)*	*Thyroxine (μg/100 ml) %*	*Cortisol (μg/100 ml) (A.M./P.M.)*
1	27	2	+	970	8.5	10.5	7.1	18.5/–
2	21	1	+	824	4.0	5.6	4.9	8.4/2.4
3	37	6	+	502	11.6	10.9	8.8	
4	19	1	–	490	6.4	7.8	8.1	14/4
5	19	Primary	–	253	9.5	7.8	5.0	15/–
6	27	7	+	229	4.0	7.0	5.0	21/8
7	21	3	+	225	9.7	13.4	7.9	21/9.5
8	27	5½	+	221	14.0	15.0	10.4	12/5.5
9	27	2	–	150	14.1	26.4	6.2	19.6/–
10	31	3	+	105	12.4	14.2	8.7	15/5
11	33	5	+	102	14.1	12.3	6.3	12/–
12	29	6	–	95	12.5	20.0	9.6	9.7/6.4
13	29	2	+	90	10.4	9.6	7.6	16.6/4
14		6	+	99	12.4	26.3	8.0	—
Normal laboratory values			+	0-20	4.6-22.0	6.5-24	4.6-10.7	5-20

TSH was normal in all patients.

Standard sella turcica x-ray films were normal in all 14 patients, while routine tomography was abnormal in two of seven patients studied. Thin-section (1 to 2 mm) polytomography (12 patients) was abnormal in 11 patients and equivocal in one patient. Carotid arteriography and pneumoencephalography, performed preoperatively in all patients, were normal. Comprehensive studies of pituitary function were conducted 4 to 6 weeks prior to operation.

Gonadotropic hormone reserve. A dosage of 100 μg of luteinizing hormone–releasing factor (LRF) (AY-24031*) was given subcutaneously to 13 of the 14 patients, whereupon serum luteinizing hormone (LH) and follicle-stimulating hormone (FSH) were assayed at −30, 0, 15, 30, 60, 120, and 240 minutes.

Growth hormone reserve. This was assessed in 13 of the 14 patients. After an overnight fast and 90 minutes following the placement of an indwelling venous catheter, regular insulin was injected intravenously in a dose of 0.1 U/kg of body weight; serum assays for growth hormone and glucose were obtained at 15 minute intervals for 90 minutes.

Assessment of hypothalamic-pituitary-adrenal axis. Plasma cortisol concentrations were determined at 0 and 90 minutes following the administration of insulin in 10 of the 13 patients in whom growth hormone secretion was studied. In two of the patients, the axis was assessed with urinary 17-hydroxycorticosteroid determination following oral metyrapone (750 mg every 4 hours for 6 doses).

Indications for surgical intervention, each weighed independently, included: (1) "significant" hyperprolactinemia (>100 ng/ml), (2) unequivocal radiographic abnormality (13 patients), (3) desire for pregnancy (seven patients).

The transsphenoidal approach to the sella was employed in all patients, and a pathologically confirmed microadenoma was identified and resected in 13, while an inferior sella diverticulum containing a minute volume of "abnormal" tissue was found in the remaining patient (Case No. 14); the tissue was removed but neither tumor nor lactotroph hyperplasia could be verified histologically.

In the 13 patients with confirmed microademonas, the surgical technique varied somewhat as experience grew. Tumor removal was effected by (1) simple suction and curettage of the tumor bed (five patients); (2) suction removal followed by placement of an ethanol-soaked pledget into the tumor cavity for 1 minute (in one patient); (3) suction and curettage of the tumor bed, with biopsy of the edges of the surrounding normal-appearing pituitary tissue (two patients); (4) suction and curettage of the tumor bed, with biopsy of the edges, followed by placement of an ethanol-soaked pledget for 1 minute in the tumor cavity (five patients). Tumor size varied from 3 to 10 mm in diameter. In Case No. 2, pleomorphism, increased mitotic activity, and mildly atypical changes were seen. In the remaining 12 patients, the histologic picture was entirely benign.

Eleven of the 13 patients with microadenomas were readmitted 10 to 14 weeks postoperatively for endocrine testing. Baseline hormonal studies (i.e., serum thyroid-stimulating hormone (TSH), prolactin, growth hormone, and plasma cortisol (A.M. and P.M.) were obtained. Gonadotropic hormone reserve, growth hormone reserve, and the hypothalamic-pituitary-adrenal axis were reassessed in all 11 patients. In the remaining

*Provided by Ayerst Labs., New York, New York.

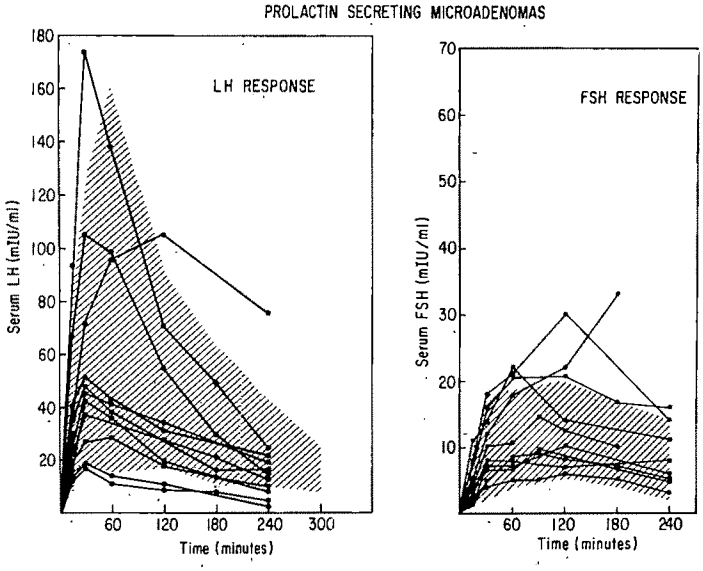


Fig. 1. Effect of LRF on serum LH and serum FSH levels in 11 women with prolactin-secreting microadenomas. The closed circles connected by lines represent the change from baseline of serum LH levels and serum FSH levels following the subcutaneous administration of 100 μg of LRF. The shaded area represents the range of response in 18 normal women studied in the early follicular phase.

two patients not admitted to the hospital, one was followed up with periodic determinations of prolactin, FSH, LH, thyroxine, and urinary 17-hydroxycorticosteroids, while the other was not tested as she conceived 4 to 5 weeks postoperatively.

Adjunctive radiotherapy (i.e., 5,000 rads) was recommended in Case Nos. 1, 2, and 3 (significant hyperprolactinemia postoperatively) and was initiated in Case Nos. 1 and 2 6 and 7 months postoperatively, respectively. In Case 3 adjunctive radiotherapy was refused. Follow-up on all patients extends from 5 months to 3 years. In Cases 3 and 6 the patients were lost to follow-up at 6 months.

Serum prolactin,[6] TSH,[7] LH,[7] FSH,[7] and growth hormone[8] were determined by radioimmunoassay. Serum thyroxine was assayed by competitive protein-binding radioassay.[9] Plasma cortisol levels were measured by competitive protein binding.[10] Laboratory values for women were: follicular phase FSH, 4.6 to 22 mIU/ml; follicular phase LH, 6.5 to 24.2 mIU/ml; prolactin, 0 to 20 ng/ml; TSH, 0 to 10 mU/ml; thyroxine, 4.6 to 10.7 μg/100 ml.

Results

The immediate postoperative course of the patients was uncomplicated with the exception of transient diabetes insipidus in four patients.

Preoperative studies. In 12 of the patients, growth hormone secretion in response to insulin-induced hypoglycemia was normal according to the criteria of Eddy and associates.[11] One patient (Case No. 4) had no response.

A normal plasma cortisol response to insulin-induced hypoglycemia (greater than twofold rise from baseline) was noted in seven of 10 women tested. In Case No. 1 the patient had no response, while the cortisol response was attenuated (less than twofold rise from baseline) in Cases No. 7 and No. 8. Adrenocorticotropic hormone (ACTH) reserve, tested in two patients (Cases 4 and 9) with metyrapone, was normal.

Eleven patients had a normal LH response to LRF (compared to early follicular phase response) while two patients had a response which was borderline low (Cases 1 and 6) (Fig. 1).

Postoperative studies. Although not shown, serum TSH, baseline growth hormone levels, thyroxine, serum LH, serum FSH, plasma cortisol levels, and/or urinary 17-hydroxycorticosteroid hormones were normal in all patients studied postoperatively. As shown in Table II, prolactin levels decreased postoperatively in all patients. Prolactin levels were above 50 ng/ml (range 112 to 427) in three patients, between 20 and 50 ng/ml in five patients, and below 20 ng/ml in the remaining five patients.

In all 11 patients studied, growth hormone response to insulin-induced hypoglycemia was normal and essentially unchanged from preoperative studies. Growth hormone reserve was not tested in the one patient in whom preoperative studies had failed to demonstrate a response to insulin-induced hypoglycemia.

Table II. Prolactin-secreting microadenoma: postoperative follow-up

Case No.	Prolactin (ng/ml)		Galactorrhea	Time to menses	Pregnancy		Follow-up (mo.)	Comment
	Preoperative	Postoperative			Desired	Achieved		
1	970	427	↓	–	+	–	24	Radiotherapy*
2	824	112	↓	–	+	–	18	Radiotherapy*
3	502	368	–	–	–	–	6	Lost to follow-up
4	490	35	↓	–	–	–	18	Recurrent tumor
5	253	45	–	–	+	–	12	Stable†
6	229	50	↓	–	–	–	6	Lost to follow-up
7	225	11.5	0	6 wk	–	–	24	Stable†
8	221	19.0	0	5 wk	–	–	12	Stable†
9	150	10.5	–	6 wk.	+	+	36	Delivery at term†
10	105	40	↓	After abortion	–	+	18	Abortion at about 10 wk.†
11	102	9	0	8 wk.	+	–	17	Stable†
12	93	20	–	4 wk.	+	–	8	Stable†
13	90	33	↓	–	+	+	18	Clomiphene, cesarean section at term
14‡	99	–						

*Prolactin levels decreasing.
†Prolactin levels stable.
‡No tumor found—diverticulum of the sella.

Table III. Surgical technique and postoperative prolactin levels

Technique	No. of patients	Prolactin level		
		> 50 ng/ml	20-50 ng/ml	< 20 ng/ml
Suction, curettage	5	2	3	-
Suction, currettage, and biopsy	2	-	1	1
Suction, ethanol pledget	1	1	-	-
Suction, curettage, biopsy, ethanol pledget	5	-	1	4

A normal plasma cortisol response to insulin-induced hypoglycemia was noted in nine patients, in two of whom an attenuated response had been demonstrated before operation. In Case No. 1 (no response preoperatively) the patient failed to respond. An attenuated response was noted in Case No. 9 (preoperative normal metyrapone testing); however, the baseline plasma cortisol level was mildly elevated and may have accounted for the failure to significantly increase plasma cortisol levels during stress.

The LH response to LRF was similar to the preoperative response in the 10 patients studied both preoperatively and postoperatively. Furthermore, the LH response in the patients in whom cyclic menses resumed and in those who remained amenorrheic was similar (Fig. 2).

As shown in Table II, galactorrhea following pituitary surgery diminished in six and completely resolved in three patients. Cyclic menses resumed in five patients in 4 to 8 weeks following operation, all with prolactin levels less than 20 ng/ml. One patient (Case No. 10) became pregnant prior to reinstitution of menses and (by uterine size) probably conceived 4 to 5 weeks postoperatively; however, the pregnancy was terminated at 11 weeks for psychosocial reasons, with the subsequent development of cyclic menses. Of the five patients with cyclic menses, three desired pregnancy; one has conceived with a normal prenatal course and delivery, while the remaining two patients (8 and 17 months after operation) have not yet conceived. Of the remaining four patients desiring pregnancy, two have had postoperative radiotherapy, and one has been lost to follow-up, while ovulation induction with clomiphene citrate in the remaining patient resulted in conception and delivery of a viable infant at term.

Follow-up has extended from 6 months to 3 years. In the three patients with prolactin levels above 50 ng/ml, radiotherapy in two of the patients has resulted in a progressive decline in prolactin levels. In the remaining five patients in whom prolactin levels were modestly elevated immediately postoperatively, i.e., 8 to 12 weeks, prolactin levels have not changed in three (6 to 18 months' follow-up), while in one patient (Case No. 4) a stable level of prolactin was maintained for 12 months with the subsequent rapid increase resulting in

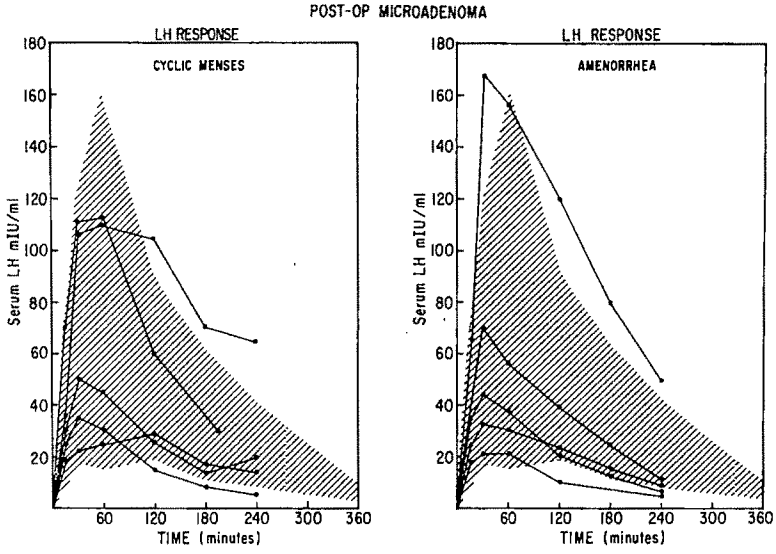


Fig. 2. Effects of LRF on serum LH levels in 10 women following resection of prolactin-secreting microadenomas. The responses (change from baseline of serum LH levels following the subcutaneous administration of 100 μg of LRF) of women with cyclic menses postoperatively are displayed on the right, while responses of those women remaining amenorrheic are displayed on the left. The shaded area represents the range of response in 18 normal women studied in the early follicular phase.

re-exploration of the sella and extirpation of a recurrent tumor with evidence of suprasellar extension. The remaining patient (Case No. 13) has only recently been delivered, and a follow-up prolactin level, obtained 4 months post partum, was normal (2.7 ng/ml).

Prolactin levels have remained normal in the five patients (8 to 36 months' follow-up) in whom initial postoperative prolactin levels were normal.

Differences in surgical technique were compared to the results obtained and are shown in Table III. In the five patients in whom tumor removal was effected by suction and curettage alone, all had elevated prolactin levels postoperatively, while four of the five patients in whom suction, curettage, biopsy of contiguous normal pituitary, and placement of an ethanol pledget into the tumor cavity were carried out were euprolactinemic postoperatively.

A comparison between preoperative prolactin levels, tumor size, and postoperative prolactin levels is shown in Table IV. Of the five patients with tumors larger than 8 mm in diameter, postoperative prolactin levels were greater than 50 ng/ml in three, between 20 and 50 ng/ml in one, and within the normal range in one patient. In contrast, four of the seven patients with tumors less than 8 mm in diameter had normal postoperative prolactin levels while three had levels between 20 and 50 ng/ml. In the four patients with preoperative prolactin levels above 300 ng/ml, postoperative prolactin levels were elevated. Postoperative prolactin levels were normal in five of the nine patients with preoperative prolactin levels below 300 ng/ml.

Table IV. Prolactin-secreting microadenoma: Prolactin levels, surgical technique, and tumor size

Case No.	*Preoperative prolactin (ng/ml)*	*Tumor size (mm diameter)*	*Surgical technique*	*Postoperative prolactin (ng/ml)*
1	970	10	S	427
2	824	10	S	112
3	502	8	S	368
4	490	10	O	35
5	253	5	S	45
6	229	6	S	50
7	225	5	O	11.5
8	221	9	O	19.0
9	150	4	O	10.5
10	105	3	S	40
11	102	3	S	9.0
12	93	7	O	20.0
13	90	3	S	33.0

S, Suboptimal; O, optimal.

Comment

Although a major neurosurgical procedure, selective removal of pituitary microadenomas is a relatively innocuous procedure, as the negligible morbidity seen in this series suggests. Despite pituitary surgery, trophic hormone function (i.e., TSH, growth hormone, and ACTH) was preserved in most instances and perhaps improved. Improvement of an attenuated cortisol re-

sponse to insulin-induced hypoglycemia following removal of prolactin-secreting microadenomas has been previously described.[12] This alteration, while interesting, defies explanation although the preoperative attenuated response seen in two of our patients may have been spurious. Although a normal gonadotropic response to LRF should reflect the integrity of the hypothalamic-pituitary-gonadal axis and provide an estimate of pituitary gonadotropin reserve, this test does not necessarily indicate normal function of the axis. The similarity of responses observed preoperatively and postoperatively and the similarity of responses (in the postoperative group) between those patients in whom cyclic menses resumed and those who remained amenorrheic appears to negate the predictive value of the LRF test.

The persistence of hyperprolactinemia in eight of the 13 patients is frankly disconcerting. Compromise of pituitary stalk function, secondary to surgical manipulation, seems an unlikely explanation, as one would expect only temporary disruption with rapid resolution. More permanent stalk damage is equally untenable, as compromise of other trophic hormones would be expected in this instance. Residual tumor seems the most probable explanation, particularly in Case Nos. 1, 2, and 3, since prolactin elevations of such magnitude could hardly be ascribed to inherent hypothalamic dysfunction. Certainly, the progressive decline in prolactin levels following radiotherapy in two of these patients further supports this hypothesis.

The modest elevations of prolactin (i.e., 20 to 50 ng) seen postoperatively in five of our patients is consistent with residual tumor but may reflect inherent hypothalamic dysfunction. Conceivably, chronic impairment of prolactin–inhibiting factor secretion could lead to moderate hyperprolactinemia or even localized adenomatous hyperplasia. Despite "removal" of an apparently focal tumor, a small number of lactotrophs may remain behind and continue to secrete prolactin unabated. The apparent stabilization of prolactin levels over a period of 6 to 18 months would be compatible with this hypothesis. On the other hand, among these five patients, tumor removal was effected in four with suction and curettage alone. Since we presently view this as less than optimal therapy, the persistence of hyperprolactinemia in these patients is considered most probably due to residual tumor, i.e., incomplete resection of the tumor margins. Certainly, the postoperative course in Case No. 4 indicates the necessity for close follow-up of all patients with modest elevation of prolactin postoperatively.

Five of the patients in this series were provided what we now regard as optimal surgical therapy: suction removal, curettage of the tumor cavity, biopsy of the surrounding normal-appearing pituitary tissue, and application of absolute ethanol to the cavity for 1 minute. Four of these patients (80%) were euprolactinemic postoperatively. This experience should be compared to that in the eight patients in whom attempted resection was less rigorous; only one of these patients (12.5%) was euprolactinemic postoperatively.

In addition to surgical technique, tumor size may be a determinant of success. In patients with tumors larger than 8 mm in diameter, only one of the five (20%) was euprolactinemic postoperatively. In contrast, among patients with tumors less than 8 mm in diameter, four of seven (57%) were euprolactinemic postoperatively.

Yet another important factor in the surgical outcome is the surgeon's personal operative experience with these lesions. Examination of results among the first 15 consecutive patients operated upon by a single person (RSK) reveals a significant chronological trend (five of these are excluded from the present series as a consequence of incomplete or short duration of follow-up); among the first three patients, one (No. 1) demonstrated marked hyperprolactinemia postoperatively while two patients (No. 5 and No. 6) demonstrated moderate persistent hyperprolactinemia (20 to 50 ng per milliliter). Among the next three patients operated upon, two (No. 10 and No. 13) demonstrated modest postoperative elevations of prolactin (both of these patients have conceived), while the third (No. 11) became euprolactinemic. Operations performed on the next nine patients resulted in persistent and significant postoperative hyperprolactinemia in two, and normal prolactin levels in the remaining seven (78% "endocrinologic cure"). It would thus appear that increasing experience with these tumors is also a major determinant of success.

Our experience then suggests that the surgical therapy of pituitary microadenomas should include thorough curettage of the tumor bed and biopsy of surrounding normal-appearing pituitary tissue, followed by application of absolute ethanol to the tumor cavity. The preservation of trophic hormone function in our patients despite biopsy and alcohol treatment of pituitary tissue further supports an aggressive approach in the treatment of these tumors. Furthermore, our experience favors early treatment of these tumors, inasmuch as the "cure" rate appears inversely related to tumor size.

Finally, improved results can be anticipated as the surgeon's experience with these tumors increases.

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Endocrine studies of normal and polycystic ovarian tissues in vitro

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The purpose of this study was to compare the steroidogenic potential of the granulosa, theca, and medullary tissues from polycystic and normal ovaries. These ovarian endocrine compartments were isolated from appropriate ovaries and were cultured in vitro for three days in the absence (control) and presence of follicle-stimulating hormone (FSH)/luteinizing hormone (LH) (1 IU/ml), N^6,O^2-dibutyryladenosine-3′:5″-cyclic monophosphoric acid (Bu_2cAMP) ($10^{-2}M$), and adrenocorticotropic hormone (ACTH) (1.3 U/ml). After the incubation, steroids in the media were measured by radioimmunoassay. Granulosa cells (10^5 cells per dish) from 4 to 7 mm follicles of normal and polycystic ovaries secreted progesterone spontaneously during the culture period and the production of progesterone spontaneously during the culture period and the production of progesterone was markedly stimulated (between tenfold and thirtyfold) by gonadotropins and Bu_2cAMP but not by ACTH. Little, if any, androgen (androstenedione, dehydroepiandrosterone, and testosterone) or estrogen (estrone and estradiol) accumulated in the media of any granulosa cell culture. The control cultures of theca tissue from normal and polycystic ovaries secreted large amounts of androstenedione and progesterone and the production of these steroids by normal and polycystic ovary theca was stimulated in most cases by LH/FSH and Bu_2cAMP but not by ACTH. Both normal and polycystic ovary theca secreted some testosterone and dehydroepiandrosterone but little, if any, estrone or estradiol accumulated in any theca culture. The medullary tissue of normal and polycystic ovaries produced only trace amounts of steroids in vitro except for the results from one polycystic ovary with hyperthecosis in which case significant quantities of C_{19} and C_{18} steroids were secreted. These experiments have demonstrated that isolated granulosa and theca cells from midantral follicles of normal and polycystic ovaries have a similar capacity to secrete C_{21} and C_{19} steroids in the absence and presence of trophic agents. Therefore, it seems probable that chronic anovulation in patients with polycystic ovaries is not caused by an obvious deficiency in the de novo steroidogenic potential of the multiple midantral follicles of the polycystic ovaries or by the absence of gonadotropin receptors on the polycystic ovary follicular cells. (AM. J. OBSTET. GYNECOL. 134:56, 1979.)

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PREVIOUS studies of protein hormone concentrations in the sera of patients with polycystic ovarian disease (PCO) have been unable to define the primary cause of this pathophysiologic state. Elevated luteinizing hormone (LH) concentrations in many PCO patients suggest that a dysfunction may exist in the hypothalamic-pituitary axis with resultant ovarian endocrine changes.[1] On the other hand, increased peripheral concentrations and production rates of steroids as well as high levels of androgens in the ovarian vein suggest that a defect exists in ovarian steroidogenesis with secondary hypothalamic-pituitary dysfunction.[2]

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In vitro studies of ovaries from PCO patients have also produced conflicting results. Two defects in ovarian steroid enzymes have been demonstrated in some PCO patients: (1) An aromatase deficiency, which could explain the increased androgen to estrogen ratio, and (2) a 3-beta-hydroxysteroid dehydrogenase deficiency which would lead to increased production of Δ5 steroids such as dehydroepiandrosterone.[3] In contrast, other investigators have been unable to define defects of steroid enzymes in the polycystic ovary and have suggested that the increased androgen production results from an increase in the amount of ovarian tissue or from the hyperactivity of some ovarian cell types.[4]

In vitro experiments using isolated ovarian cells have provided important information regarding the steroidogenic potential of these ovarian endocrine compartments during different reproductive states.[5–7] In the present study, we have applied such in vitro techniques to the polycystic ovary for the purpose of determining whether chronic ovulation in the patient with PCO is related to deficiencies in the steroidogenic potential of the developmentally arrested midantral follicles in the polycystic ovary. To meaningfully interpret the data, we have performed similar experiments using cells from normal ovaries and used these data as a standard to which the observations from polycystic ovaries are compared.

Material and methods

Normal patients. Ovarian fragments were obtained from two patients undergoing laparotomy for nonendocrine reasons. Patient M. H. was a 30-year-old woman, gravida 1, para 1, who had experienced regular menses every 27 days prior to undergoing laparotomy at day 18 of the cycle. One ovary contained a fresh corpus luteum and was not used in this study. A wedge of tissue was removed from the opposite ovary, part of which was sent to the pathologists for tissue study and the remaining portion was placed in cold McCoy's 5a medium for in vitro studies. Patient S. B. was a 38-year-old woman, gravida 4, para 3, abortions 1, with regular menses occurring every 29 days. On day 8 of the menstrual cycle, the patient underwent hysterectomy and bilateral salpingo-oophorectomy for uterine leiomyomas. Portions of both ovaries were removed for experimental purposes and the remainder was fixed for histologic examination. The ovarian sections from both ovaries were judged to be normal.

Patients with PCO. Ovarian tissue was obtained from two patients with documented PCO. Patient M. D. was a 30-year-old woman, gravida 2, para 2, with obesity, hirsutism, and oligomenorrhea of increasing severity. Serum LH was 72 mIU/ml; follicle-stimulating hormone, (FSH) 6 mIU/ml; and testosterone concentration, 900 pg/ml (normal is between 300 and 750 pg/ml). 17-Ketosteroids were 10 mg/24 hours. Hysterectomy and bilateral salpingo-oophorectomy were performed for sterilization. Both ovaries were markedly enlarged (measuring 4 by 4 by 5 cm) and were surrounded by a thickened tunica albuginea with multiple graafian follicles.

Patient M. F. was a 33-year-old, nulligravid woman with documented PCO who underwent bilateral ovarian wedge resection after failing to respond to clomiphene citrate. Prior to surgery, levels of LH and FSH were 60 and 10 mIU/ml, respectively. Total serum testosterone was 850 pg/ml. Urinary 17-ketosteroids were 13 mg/24 hours. Both ovaries (measuring 4 by 4 by 5 cm) were covered with a thickened capsule and had numerous graafian follicles lining the subcortical surface.

Culture medium. Ovarian tissue was cultured in 6 ml of McCoy's 5a medium (modified, GIBCO), containing L-glutamine (2 mM, penicillin (100 U/ml), streptomycin sulfate (100 μg/ml), and 10% serum obtained from a patient with Sheehan's syndrome. This culture medium contained less than 20 pg/ml of progesterone (P), androstenedione (A), dehydroepiandrosterone (DHEA), testosterone (T), estrone (E_1), and estradiol (E_2). All cultures were maintained for 72 hours in a 95% air–5% carbon dioxide incubation at 37° C.

Each set of granulosa, theca, and medullary cultures was incubated either as a control or with one of the following agents: 1 IU/ml LH/FSH (Pergonal, Cutter Laboratories), 1 mM N^6O^2-dibutyryladenosine-3′:5″-cyclic monophosphoric acid (Bu_2cAMP, Sigma Chemicals), or 1.3 U/ml highly purified adrenocorticotropic hormone (ACTH) (Acthar, Armour Pharmaceutical Company). After 72 hours, the culture media were collected and stored at −20° C until analyzed for steroids by radioimmunoassay.

Granulosa cell cultures. Sets of five follicles (4 to 7 mm in diameter) from normal and polycystic ovaries were dissected intact from the ovarian tissue and then placed into separate dishes containing 5 ml of McCoy's medium. Each follicle was punctured with an iris knife and the granulosa cells were expressed into the media. By means of an orally controlled micropipette, the granulosa cells were transferred to a 15 ml conical centrifuge tube and spun at 250 × g for 10 minutes. The pellet was resuspended in a known volume of culture medium, and 100 μl of the cell suspension (50,000 cells) was added to appropriate 60 by 15 mm Falcon tissue culture dishes.

Theca and medullary cultures. After granulosa cells were removed, the remaining portions of the normal

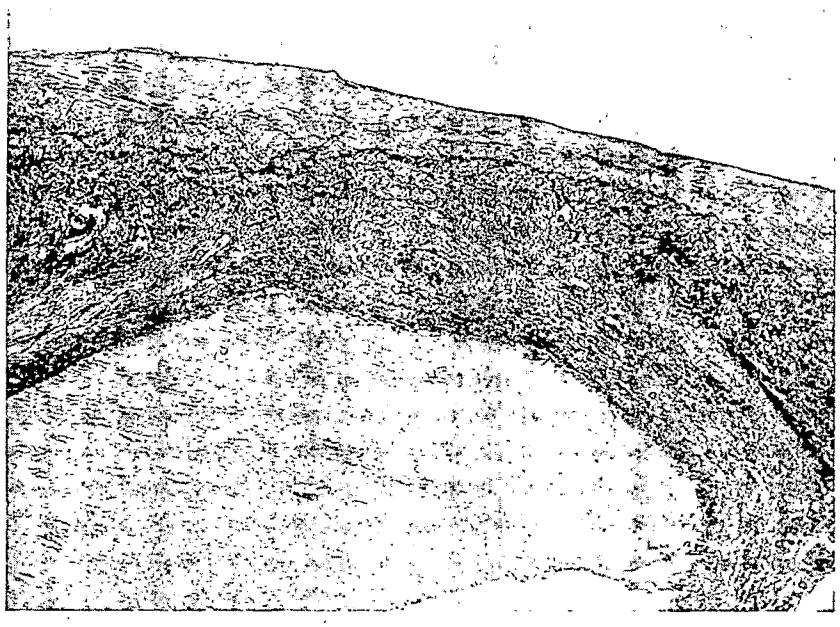


Fig. 1. Section of polycystic ovary, containing markedly thickened ovarian capsule with multiple subcapsular graafian follicles, with pronounced hyperplasia of the theca compartment.

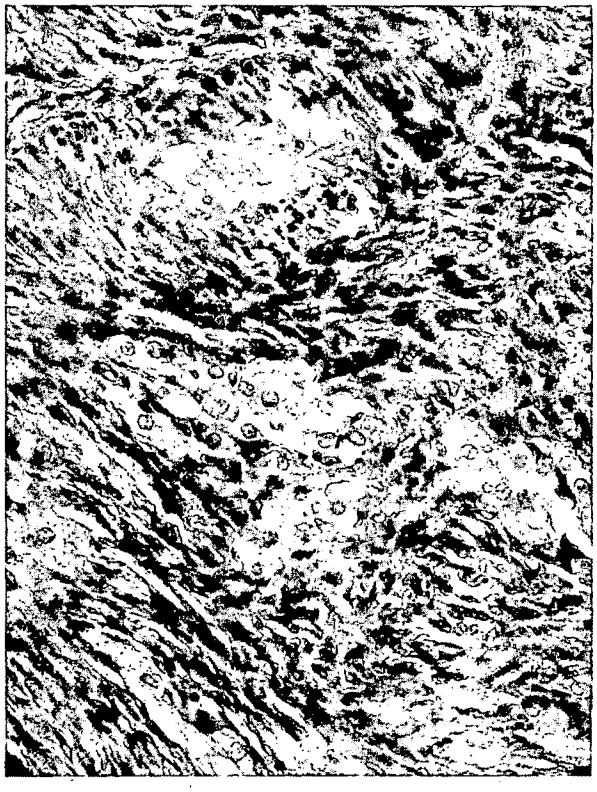


Fig. 2. Section of ovaries of Patient M. D., containing clusters of large epithelioid cells with eosinophilic cytoplasm scattered throughout the medullary stroma, which is suggestive of hyperthecosis.

and polycystic follicles were cut into four pieces and then scraped with an iris knife to remove the remaining granulosa cells from the basement laminae.[8] From this pool of normal and polycystic ovarian theca, three pieces (each 3 mm in diameter) were selected at random and placed into appropriate tissue culture dishes.

The medullary portions of the control and the polycystic ovaries were dissected free of cortical tissues and cut into pieces 3 mm in diameter. Ten pieces of control and polycystic medullary tissue were placed into appropriate culture dishes and incubated for 72 hours. All experiments (granulosa, theca, medullary tissue) were performed in quadruplicate.

Tissue study. Sections of normal and polycystic ovaries were obtained at the time of surgery. At the end of each experiment, representative cultures were prepared for tissue study as described previously.[5]

Steroid chromatography and radioimmunoassay. The chromatographic procedures and radioimmunoassays for progesterone, androstenedione, dehydroepiandrosterone, estrone, and estradiol-17β have been described previously.[9, 10] Dehydroepiandrosterone was measured according to the procedures described by Buster and Abraham.[11] Briefly, steroids were extracted from 1 ml of culture medium with 5 ml of fresh anhydrous diethyl ether. The aqueous phase was rapidly frozen with solid carbon dioxide and the organic phase was decanted and the ether evaporated under nitrogen. The residue was applied to Celite columns with

Table I. De novo steroid production by cultured granulosa cells of normal and polycystic ovaries*

Patient	*Control*	*FSH/LH*	*Bu_2cAMP*	*ACTH*
Normal ovaries:				
Patient S. B. (day 8 of cycle)				
P	0.6 ± 0.2†	60.8 ± 1.5‡	71.5 ± 3.8‡	1.6 ± 1.0
A	—§	0.6 ± 0.1	0.7 ± 0.2	—
T	—	—	—	—
DHEA	—	0.3 ± 0.1	0.9 ± 0.2	1.2 ± 0.7
E_1	—	—	—	—
E_2	—	—	—	—
Patient M. H. (day 18 of cycle)				
P	1.8 ± 1.0	15.3 ± 5.5	62.8 ± 23.5‡	5.1 ± 2.9
A	—	—	—	—
T	—	—	—	—
DHEA	—	—	—	—
E_1	—	—	—	—
E_2	—	—	—	—
Polycystic ovaries:				
Patient M. D.:				
P	2.1 ± 1.0	35.0 ± 1.0‡	39.5 ± 1.1‡	5.9 ± 0.6‡
A	—	0.7 ± 0.2	1.3 ± 0.4	0.4 ± 0.1
T	—	—	—	—
DHEA	—	—	—	—
E_1	—	—	—	—
E_2	—	—	—	—
Patient M. F.:				
P	2.7 ± 1.1	104.1 ± 13.5‡	97.0 ± 4.7‡	5.9 ± 0.2‡
A	—	0.7 ± 0.1	0.7 ± 0.1	0.2 ± 0.1
T	—	—	—	—
DHEA	0.3 ± 0.1	0.5 ± 0.1	0.7 ± 0.3	0.2 ± 0.1
E_1	—	—	—	—
E_2	—	—	—	—

*Each culture dish contained 3 ml cultured media and ~10^5 granulosa cells from secondary follicles between 4 and 7 mm in diameter.

†Values expressed as ng/ml/3 days in vitro (mean ± SEM of quadruplicate determinations).

‡Significantly greater than control values, $p < 0.05$, Student's t test.

§Nondetectable.

ethylene glycol as a stationary phase in 0.2, 0.2, and 0.3 ml of isooctane. The steroids measured were obtained from three elution fractions. Fraction I, containing progesterone and androstenedione, was eluted with 4.0 ml of isooctane. Fraction II, containing estrone and dehydroepiandrosterone, was eluted with 4.0 ml of 15% ethyl acetate in isooctane. Fraction III, which contained estradiol-17β, was eluted with 3.5 ml of 40% ethyl acetate in isooctane. The collection vials were evaporated to dryness under nitrogen and resuspended in 1.5 ml of 0.1M phosphate buffer, pH 7.0, containing 0.1% gelatin, and aliquots were taken for determination of recovery and radioimmunoassay.

The progesterone antibody demonstrated a cross-reactivity of 100% with progesterone, 35% with deoxycorticosterone, 7% with 20α-dihydroxyprogesterone, 5% with A and T, and less than 1% with other C_{21}, C_{19}, and C_{18} steroids. The antibody for A cross reacted 100% with A and 16% with DHEA but less than 1% with other steroids. The DHEA antibody cross reacted 100% with DHEA and DHEA sulfate and 12.5% with A. A nonspecific, total estrogen antibody was used to detect estrone but this antibody cross reacted less than 0.01% with C_{21} and C_{19} steroids. The estradiol antibody was more specific, cross reacting 100% with estradiol-17β, 3.0% with estrone and estriol, but less than 0.1% with other steroids. T in the media was measured directly (following extraction) using T antiserum (S No. 250, 11–bovine serum albumin) supplied by Dr. J. Bain. In addition to 100% cross-reactivity with testosterone, this antibody showed a high cross reaction with dihydrotestosterone (72%) but did not cross react (less than 1%) with other C_{18}, C_{19}, and C_{21} steroids.

The interassay coefficient of variation for all steroids was less than 17% and the intra-assay coefficient of variation was less than 9%.

Results

Ovarian tissue study. Examination of sections obtained from ovaries of both patients with PCO indi-

Table II. De novo steroid production by isolated thecal tissue of normal and polycystic ovaries*

Patient	*Control*	*FSH/LH*	*Bu_2cAMP*	*ACTH*
Normal ovaries:				
Patient S. B. (day 8 of cycle)				
P	1.5 ± 0.2†	10.0 ± 2.4‡	10.0 ± 0.3‡	1.6 ± 0.2
A	26.5 ± 3.0	31.9 ± 3.5	22.3 ± 0.8	27.3 ± 0.8
T	2.6 ± 0.4	3.0 ± 0.3	2.9 ± 0	3.2 ± 0.6
DHEA	2.4 ± 0.1	3.1 ± 0.1‡	3.3 ± 0.2‡	3.3 ± 0.1‡
E_1	—§	0.4 ± 0.1	—	—
E_2	—	1.0 ± 0.1	0.5 ± 0.2	—
Patient M. H. (day 18 of cycle)				
P	29.9 ± 5.7	86.7 ± 15.9‡	28.5 ± 14.9	15.3 ± 2.4
A	71.3 ± 11.7	157.5 ± 0.5‡	85.3 ± 5.6	91.5 ± 24.0
T	5.6 ± 1.7	12.6 ± 3.9	8.1 ± 0.2	6.1 ± 1.5
DHEA	3.0 ± 0.8	3.2 ± 1.1	4.1 ± 1.4	3.2 ± 0.9
E_1	—	0.5 ± 0.1	—	0.3 ± 0.1
E_2	0.7 ± 0.3	2.2 ± 0.4‡	0.6 ± 0.3	0.4 ± 0.3
Polycystic ovaries:				
Patient M. D.				
P	7.0 ± 0.7	84.1 ± 13.2‡	100.9 ± 36.1‡	14.0 ± 3.8
A	41.0 ± 9.6	61.7 ± 19.2	52.7 ± 12.8	13.2 ± 3.8
T	4.8 ± 0.8	7.9 ± 0.8‡	8.5 ± 1.2‡	2.3 ± 0.7
DHEA	3.8 ± 0.6	4.8 ± 1.4	7.0 ± 0.6‡	3.0 ± 1.1
E_1	0.3 ± 0.2	0.4 ± 0.2	0.4 ± 0.2	—
E_2	0.8 ± 0.3	1.3 ± 0.1	1.7 ± 0.3	0.9 ± 0.4
Patient M. F.				
P	24.7 ± 3.6	136.7 ± 9.3‡	68.3 ± 4.5‡	28.5 ± 2.1
A	13.6 ± 1.6	65.4 ± 9.4‡	100.1 ± 10.1‡	13.1 ± 1.6
T	5.1 ± 0.8	5.7 ± 0.2	6.8 ± 1.6	3.4 ± 0.7
DHEA	4.4 ± 1.0	6.5 ± 0.9	11.5 ± 0.6‡	2.2 ± 0.6
E_1	0.5 ± 0.2	0.9 ± 0.1	0.4 ± 0.2	0.9 ± 0.2
E_2	1.0 ± 0.3	1.2 ± 0.5	1.0 ± 0.4	1.2 ± 0.2

*All dishes contained 3 ml of culture media with three pieces (3 mm in diameter) of theca tissue obtained from secondary follicles 4 to 7 mm in diameter.

†All values expressed in ng/ml/3 days (mean ± SEM of quadruplicate determinations).

‡Significantly greater than control values, $p < 0.05$, Student's t test.

§Nondetectable.

cated the presence of a markedly thickened ovarian capsule with multiple subcapsular graafian follicles (4 to 7 mm in diameter), with pronounced hyperplasia of the theca compartment (Fig. 1). Ovaries of Patient M. D., but not Patient M. F., contained clusters of large epithelioid cells with eosinophilic cytoplasm scattered throughout the medullary stroma, which is suggestive of hyperthecosis (Fig. 2). The ovaries of both control patients were grossly and microscopically normal. In Patient M. H., the left ovary contained a fresh corpus luteum.

In vitro tissue study. The granulosa cells from both normal and polycystic ovaries attached to the culture dish within the first 24 hours in vitro and grew primarily as colonies of epithelial cells. After 72 hours in vitro, the normal and polycystic granulosa cells treated with gonadotropins and Bu_2cAMP underwent luteinization and developed large numbers of osmiophilic lipid droplets, and control and ACTH-treated granulosa cells appeared as typical nonluteinized cells.

The morphologic and cytologic characteristics of normal and polycystic theca tissue in vitro are similar to those reported in organ cultures of human,[6] rabbit,[12] and hamster[7] theca elements. In the theca cultures, the explants had attached to the culture dish by 3 days and fibroblasts and epithelial cells were migrating from the explants. No obvious differences were observed between control and hormone-treated explants. Similar results were obtained in the cultures of normal and polycystic medullary tissue.

Steroid production in vitro. The steroids secreted into the media by granulosa, theca, and medullary tissue of normal and polycystic ovaries are presented in Tables I, II, and III, respectively.

As shown in Table I, control cultures of granulosa cells from normal follicles 4 to 7 mm in diameter of patients during the follicular and luteal phases of the cycle spontaneously secreted low levels of progesterone. In both cases, the production of progesterone by the normal granulosa cells was stimulated approximately tenfold by FSH/LH or Bu_2cAMP, but ACTH was without effect. Little, if any, A, DHEA, T, E_1, or E_2

Table III. De novo steroid production by isolated medullary tissue of normal and polycystic ovaries*

Patient	*Control*	*FSH/LH*	*Bu_2cAMP*	*ACTH*
Normal ovaries:				
Patient S. B. (day 8 of cycle)				
P	—†	—	—	0.4 ± 0.2
A	—	—	—	—
T	—	—	—	—
DHEA	0.4 ± 0.1‡	0.8 ± 0.5	0.4 ± 0.3	0.3 ± 0.1
E_1	—	—	—	—
E_2	—	—	—	—
Patient M. H. (day 18 of cycle)				
P	0.4 ± 0.1	0.5 ± 0.1	0.4 ± 0.1	1.5 ± 0.1§
A	—	0.3 ± 0.1	0.3 ± 0.1	1.1 ± 0.4
T	—	—	—	0.3 ± 0.1
DHEA	0.6 ± 0.1	1.3 ± 0.2§	3.5 ± 0.1§	2.0 ± 0.1§
E_1	0.3 ± 0.1	0.4 ± 0.2	0.2 ± 0.1	0.4 ± 0.1
E_2	—	—	—	—
Polycystic ovaries:				
Patient M. D.				
P	3.6 ± 2.1	6.0 ± 0.9	11.3 ± 6.5	2.5 ± 0.7
A	7.8 ± 5.2	4.0 ± 1.2	21.4 ± 17.4	3.7 ± 0.8
T	4.6 ± 0.6	7.7 ± 0.6§	6.1 ± 1.5	4.1 ± 0.9
DHEA	5.9 ± 1.1	6.7 ± 0.6	13.8 ± 3.8	7.4 ± 1.3
E_1	0.3 ± 0.1	0.3 ± 0.1	—	0.2 ± 0.1
E_2	0.4 ± 0.3	—	0.3 ± 0.1	—
Patient M. F.				
P	—	—	—	0.6 ± 0.1
A	0.5 ± 0.2	0.5 ± 0.2	0.7 ± 0.2	0.7 ± 0.1
T	—	—	—	—
DHEA	0.3 ± 0.1	0.2 ± 0.1	0.2 ± 0.1	0.3 ± 0.1
E_1	—	—	—	—
E_2	—	—	—	—

*All dishes contained 3 ml of culture media and 10 pieces of medullary tissue 3 mm in diameter.
†Nondetectable.
‡Values expressed as ng/ml/days in vitro (mean ± SEM quadruplicate determinations).
§Significantly greater than control values, $p < 0.05$, Student's t test.

accummulated in the media of any normal granulosa cell culture. In a parallel set of experiments (Table I) similar results were obtained with cultured granulosa cells from 4 to 7 mm follicles of polycystic ovaries. The only obvious difference between the normal and polycystic granulosa cell cultures was an apparent ACTH stimulation of progesterone secretion by the polycystic granulosa cells.

Table II shows the steroid hormones produced by the isolated theca tissue obtained from follicles 4 to 7 mm in diameter of normal and polycystic ovaries. The control pieces of normal theca secreted large amounts of A, some P and T, but little if any E_1 or E_2. Addition of LH/FSH caused a marked stimulation in A and P secretion by theca from Patient M. H. but was less effective in stimulating the production of these hormones in the theca from Patient S. B. Addition of Bu_2cAMP or ACTH in the normal theca cultures produced stimulatory effects. A slight stimulatory effect of LH/FSH upon estrogen production by the theca of both the normal patients was observed. In general, similar results were obtained with isolated theca fragments obtained from 4 to 7 mm follicles of patients with PCO. The principal steroids secreted by polycystic theca were A and P and the production of these steroids was stimulated by LH/FSH and/or Bu_2cAMP but not by ACTH. Although low levels of estrogens were detected in the polycystic theca cultures, no stimulatory effect of estrogen secretion was obtained by the added trophic agents.

As shown in Table III, control and experimentally treated cultures of medullary tissue from both normal and polycystic ovaries secreted very little, if any, steroids in vitro. However, in one case, the medullary tissue from Patient M. D. with hyperthecosis secreted relatively large amounts of all steroids (except estrogens) during the 3 day incubation and the production of these steroids appeared to be stimulated slightly by Bu_2cAMP but not by LH/FSH or ACTH.

Comment

These observations have shown that there is no obvious difference between the de novo steroidogenic potentials of the endocrine cells (isolated theca and granu-

losa cells) of the midantral follicles (4 to 7 mm in diameter) of normal and polycystic ovaries. During a 3 day incubation in the presence and absence of trophic agents, the steroidogenic profiles of the normal and polycystic follicular tissues were found to be similar, both qualitatively and quantitatively. On the basis of these findings, it would seem that the cessation of follicle growth and maturation in the polycystic ovaries is not caused by an obvious deficiency in the development of the endocrine potentials of the granulosa and theca cells. Therefore, these findings indicate that follicle development up to the midantral stage is probably normal in the polycystic ovary and suggest that the cessation of follicle maturation at the midantral stage may not be related to an inherent developmental abnormality in the theca and granulosa cells of the polycystic follicles. Since FSH has been shown to be essential for the continuation of normal follicle maturation to the preovulatory stage,[13] it is possible that defective secretion of FSH in patients with PCO is the principal cause of the cessation of follicle development in the polycystic ovary.

The granulosa cells from midantral follicles of both normal and polycystic ovaries undergo morphologic luteinization and secrete increased amounts of P in response to gonadotropins and Bu_2cAMP in vitro. On a per-cell basis, these normal and polycystic granulosa cells secreted comparable amounts of progestin during the 3 day incubation period. As expected, none of the normal and polycystic granulosa cell cultures secreted significant amounts of androgens and estrogens in vitro.[8, 13, 14] The absence of a detectable effect of exogenous ACTH upon normal and polycystic granulosa cell function suggests that ACTH may not modulate human granulosa cell function; however, more experiments are necessary to establish this with certainty. The present morphologic and biochemical findings with cultured human granulosa cells are consistent with previous observations on the behavior of undifferentiated human granulosa cells from medium-size antral follicles.[15] Based on our present findings, it seems likely that the developmental state of the granulosa cells in the midantral follicles of polycystic ovaries is similar to that of normal granulosa cells in medium-size follicles of normal ovaries, at least in terms of their ability to respond to gonadotropins and secrete P in vitro.

The theca tissue from treated and control medium follicles (4 to 7 mm in diameter) of normal and polycystic ovaries secreted primarily A during the 3 day culture period. This finding is consistent with previous observations that the theca interna is principally an androgen-producing tissue.[12–14] Although it was not possible in the present experiments to determine the exact number of theca interstitial cells in any of the cultured theca explants, it is of interest that, in general, the androgenic capacity was quite similar in cultures of polycystic and normal theca. Although one must be cautious, the present data suggest that the capacity of the polycystic and normal theca of midantral follicles to secrete A in vitro is comparable. The androgen production by normal theca cells was stimulated following treatment with gonadotropin and/or Bu_2cAMP; however, the data were variable. In general, this result is consistent with previous reports that androgen production by theca cells is stimulated by LH and cyclic adenosine monophosphate.[12] It is of interest that the control gonadotropin-treated cells of both normal and polycystic theca produced very little, if any, E_1 and E_2 during the 3 day incubation. This finding is consistent with previous studies which have shown that the theca compartment has a relatively limited capacity to aromatize androgen into estrogen in vitro.[12, 14, 16] Therefore, our present in vitro results are not inconsistent with the current two-cell theory for estrogen production by the follicle in which the theca cells produce androgens which diffuse into the granulosa cells where they are aromatized into estrogen.[16]

In our experiment, the only obvious difference observed between the steroidogenic potentials of the endocrine compartments of the normal and polycystic ovaries was in the steroidogenic response of the medullary tissue obtained from Patient M. D. In this study, the isolated polycystic medullary tissue secreted levels of androgens and P higher than those of normal medullary tissue. Clusters of steroid-secreting–like cells (suggestive of hyperthecosis) were found in the medullary tissue of the polycystic ovary from Patient M. D. Although the nature of the steroid-secreting cells in the medulla of polycystic ovaries is unknown, it appears from our data that such cells are predominantly androgen producing and therefore resemble, endocrinologically, the steroid-secreting cells found in the theca interna.

Recently, evidence has been reported for the existence of 11β-hydroxylase activity[17] and glucocorticoid production[18] in polycystic ovaries. This observation raises the possibility that adrenal-like steroid-secreting cells exist in the medulla of some polycystic ovaries with hyperthecosis. In view of the possibility that glucucorticoid production may be the abnormality of some polycystic ovaries with hyperthecosis, we investigated the effects of ACTH on the cellular compartments of the polycystic ovaries and compared the results with those obtained from normal ovarian tissue. No consistent trophic effect of ACTH was demonstrated. The sporadic significant differences between some steroids

in response to ACTH and their control cultures are likely due to minimal gonadotropin contamination of the ACTH preparation or small variation in tissue size.

In summary, our results suggest that the steroidogenic capacity of isolated granulosa and theca cells of midantral follicles (4 to 7 mm in diameter) of polycystic ovaries is comparable to that of normal granulosa and theca cells from midantral follicles of normal ovaries. Therefore, these findings strongly suggest that the midantral follicles of polycystic ovaries are normal. If this is indeed true, then chronic anovulation in the patient with polycystic ovaries may not be causally connected with an inherent endocrine abnormality in the theca and granulosa cells of the developing follicle in the polycystic ovary.

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Lower esophageal sphincter pressure during the normal menstrual cycle

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Lower esophageal sphincter pressure (LESP), basal gastric pH, and plasma levels of gastrin, estradiol, and progesterone were determined in ten women known to have normal menstrual cycles. All determinations were performed both during the follicular phase (Days 2 to 8) and during the luteal phase (Days 20 to 30). In addition, an intraluminal pH probe placed 5 cm. above the lower esophageal sphincter was used to test for the presence of acid reflux in response to three provocative procedures. LESP during the follicular phase was 19.0 ± 1.5 mm. Hg (mean ± S.E.M.) and during the luteal phase 16.5 ± 1.3 mm. Hg ($p < 0.01$). Basal gastric pH and plasma gastrin levels were similar at both times. Plasma estradiol in the follicular phase (76.1 ± 7.0 pg. per milliliter) increased twofold during the luteal phase (159.0 ± 6.0) ($p < 0.01$). Plasma progesterone increased from a level of 1.5 ± 0.8 ng. per milliliter during the follicular phase to 19.2 ± 4.2 during the luteal phase. Coincident with these changes in LESP and increases in steroid levels, acid reflux was detected in five women during the luteal phase but was present in only one during the follicular phase. (AM. J. OBSTET. GYNECOL. 134:64, 1979.)

PREGNANT WOMEN experience a variety of upper gastrointestinal complaints. These include heartburn, nausea, and early satiety which are commonly ascribed to the syndrome of "morning sickness." Despite their frequency the pathophysiologic basis for the increased incidence of these complaints during pregnancy is poorly understood.

Although the regulating role of estrogens and progesterone in regard to the contractile and bioelectrical activities of myometrium[1, 2] have been studied in detail, remarkably little has been studied relative to the effect of these sex steroids on gastrointestinal muscle.

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Relative to this question, recent in vitro studies have shown progesterone, but not estrogens, to reduce the tension which can be achieved in smooth muscle strips from the lower esophageal sphincter of the opossum in response to electrical, neurotransmitter and gastrointestinal hormonal stimuli.[3, 4] Moreover, recent studies in vivo have suggested a role for either progesterone alone or the combination of a potent estrogen followed by progesterone given sequentially as being responsible for a reduction in lower esophageal sphincter pressure (LESP) in pseudopregnant women and animals.[5, 7]

As a direct extension of these earlier studies, we have asked the question, might not the same sequential changes in plasma levels of steroids which occur during the normal menstrual cycle, albeit to a much lesser degree than during pregnancy, reduce LESP of women during the luteal phase as compared to the follicular phase of the menstrual cycle. The purpose of the present study was therefore to: (1) compare LESP in normal menstruating women during the follicular phase (Days 2 to 8) and during the luteal phase (Days 20 to 30) of the menstrual cycle, and (2) determine whether changes in plasma sex steroid levels occurring as a result of ovulation might correlate with measured changes in LESP.

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Methods

Volunteers studied. Ten young adult normally menstruating women with a mean age of 24.6 ± 1.8 (S.E.M.) years (range 20 to 37) and known not to have been using oral contraceptives within a period of at least three months prior to their participation in this study were evaluated. Nine of the ten volunteers studied denied any prior history of symptomatic heartburn or other gastrointestinal disease. Before each study, informed consent was obtained from each volunteer. Moreover, before the study was initiated, approval was obtained from the Human Research Review Committee of the University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania.

Intraluminal pressure measurement. All studies were performed in the Gastrointestinal Laboratory of the Presbyterian–University Hospital of the University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania. All volunteers were studied in a supine position. Three water-filled polyvinyl tubes, 1.4 mm. in internal diameter, were combined with pH electrode as a single manometric tube. The tube was inserted into the stomach and slowly withdrawn at 1 cm. intervals with initial identification of the LES as an area of localized high pressure which relaxes with swallowing. The side openings of the pressure-transmitting catheters measured 1.3 mm. in diameter and were placed at 5 cm. intervals. Intraluminal pressure was measured as pressure transmitted via these water-filled catheters to external pressure transducers (Statham 18429P 23AC) and recorded on a multichannel polygraph recorder (Grass 29349B). Each catheter was infused with distilled water at a constant rate of 0.5 ml. per minute. Sphincter pressure utilized for analysis was recorded in millimeters of mercury at the end of inspiration using the rapid pull through technique (0.5 cm. per second) with intragastric pressure used as zero reference. The mean of three individual measurements of LESP made during a single pull through, and repeated for a total of three separate complete pull throughs, was used for statistical comparisons. At the perfusion flow rate used, the performance characteristics of the manometry equipment used in our laboratory detect changes in esophageal pressure at a rate of 70 mm. Hg per second.

Procedures. All studies were performed in the morning after an overnight fast. Each volunteer was studied twice, once in the follicular phase (Days 2 to 8) and once in the luteal phase (Days 20 to 30) of one or two consecutive menstrual cycles. Day 1 was defined as the first day of menstrual bleeding. Six volunteers were first studied in the follicular phase and subsequently studied in the luteal phase, while four volunteers were first studied in the luteal phase and subsequently studied in the follicular phase with the order being determined by the convenience of the volunteer. The investigator was blinded as to the sequence of the studies for a given volunteer until completion of both studies. Before each study, 20 c.c. of blood was drawn for determination of plasma levels of gastrin, estradiol, and progesterone. Basal gastric pH was recorded at the start of each motility study.

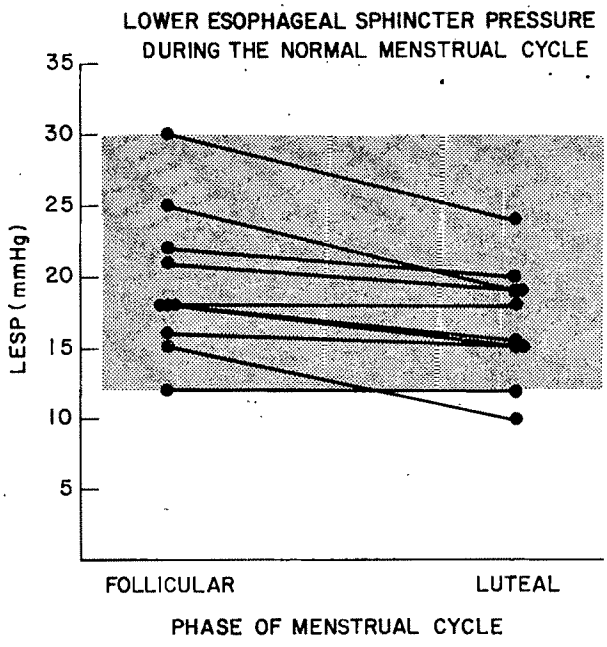


Fig. 1. Lower esophageal sphincter pressure during the follicular and luteal phases of the female volunteers studied. The solid lines connect the pressures for an individual volunteer. The shaded area is the range of values for normal women in our laboratory without attention to the menstrual cycle.

The presence of reflux was evaluated in each volunteer at the end of each study. Reflux was considered present when following the instillation of 100 c.c. of 0.1N HCl into the stomach, acid (pH <4.0) was detected by an intraluminal pH probe positioned 5 cm. above the LES with the subject in the supine position during any of the following three provocative procedures: (1) sniffing against a closed nose and mouth, (2) prolonged Valsalva maneuver, and/or (3) prolonged straight leg raising.

Plasma gastrin. Blood for plasma gastrin was obtained from each fasting volunteer before each study. Plasma was immediately separated and stored frozen at −20° C. until assayed. All gastrin determinations were performed in duplicate in a single assay by a radioimmunoassay method.[8] The sensitivity of the gastrin assay was 10 pg. per milliliter with an intra-assay variation of less than ten per cent.

Table I. Plasma gastrin, estradiol, and progesterone levels in the volunteers studied during the two phases of the menstrual cycle

	Follicular phase	*Luteal phase*
Gastrin (pg./ml.)	76 ± 3.0	81 ± 4.0
Estradiol (pg./ml.)	76.1 ± 7.0*	159.0 ± 6.0
Progesterone (ng./ml.)	1.5 ± 0.8*	19.2 ± 4.2

*$p < 0.01$.

Plasma steroids. Fasting blood for plasma estradiol and progesterone was obtained from each fasting volunteer before each study. Plasma was immediately separated and stored frozen at −20° C. until assayed using radioimmunoassay methods.[9, 10] All samples were run in duplicate in a single assay thus avoiding any interassay variation. Intra-assay variation of the radioimmunoassay for each steroid was less than ten per cent. The detection limit of the estradiol assay was 1.0 pg. and the detection limit of the progesterone assay was 10 pg.

Interpretation of data. All manometric tracings and seum samples were coded and read or analyzed blindly after all the studies were completed. The Student t test for paired data was used for statistical analysis.

Results

The sphincter pressures recorded during the follicular and luteal phases of the menstrual cycle for each patient are shown in Fig. 1. The mean pressure ± S.E.M. during the follicular phase was 19.0 ± 1.5 mm. Hg with a range from 12.0 to 30.0 mm. Hg. The mean pressure during the luteal phase was 16.5 ± 1.3 mm. Hg with a range from 10.0 to 26.0 mm. Hg. The difference in LESP recorded between the follicular and luteal phase of these ten volunteers was significantly different at the $p < 0.01$ level. All pressures but one were within the range of values for normal women without regard to menstrual cycle changes in our laboratory. The only pressure recorded outside the normal range for LES pressure was obtained during the luteal phase of the individual volunteer's menstrual cycle. Unprovoked symptomatic and pH probe positive reflux was present in only one volunteer studied during the follicular phase (the only volunteer who had an LESP below the normal range). The other nine volunteers failed to demonstrate reflux under either basal conditions or in response to the three provocative stimuli utilized. During the luteal phase symptomatic reflux was present in the same volunteer who had symptoms during the follicular phase but was also pH probe positive in four additional volunteers in response to one or more of the three provocative stimuli but not under basal unprovoked conditions.

Mean basal gastric pH during the follicular phase (2.9 ± 0.2; range 2.0 to 4.0) and luteal phase 3.3 ± 0.3; range, 2.3 to 5.2) of the menstrual cycles did not differ. Mean fasting gastrin concentrations during each of the phases of the menstrual cycle are shown in Table I. Similarly, mean fasting plasma estradiol and progesterone levels during the two phases of the menstrual cycle are shown in Table I. The mean progesterone level during the follicular phase was 1.5 ± 0.8 ng. per milliliter while a tenfold mean increase was observed during the luteal phase (19.2 ± 4.2 ng. per milliliter), when LESP was observed to decline.

Comment

This study documents a small but statistically significant reduction in LESP in normal women during the luteal phase of the menstrual cycle compared to LESP recorded in the follicular phase of these same volunteers. Coincident with the observed reduction in LESP, and as a direct consequence of ovulation, plasma progesterone levels were observed to increase during the luteal phase from levels observed during the follicular phase. Thus, the changes in progesterone levels and in LESP which were observed in this study, although not shown to be directly related, are consistent with previous reports in which progesterone has been shown to directly reduce LESP[3, 4, 7] in vitro. Moreover, these results are consistent with those previously reported in women[4, 6] and animals[7] which demonstrate that coincident with a sequential estrogen-progesterone exposure such as occurs during pregnancy and with the use of sequential oral contraceptive agents, LESP declines.

The observed decline in LESP of these normal volunteers during the luteal phase compared to LESP during the follicular phase, however, was small. Thus, only one of the subjects studied had an LESP recorded outside and below the range for normal. It is not surprising, therefore, that the frequency of symptomatic heartburn has not been reported previously to be increased in women during the luteal phase compared to the follicular phase of the menstrual cycle. When provocative tests were utilized to evaluate for the presence of stress-induced reflux, however, five of the ten women we studied had pH probe–positive reflux (only one was symptomatic) during the luteal phase compared to only one during the follicular phase. It is not unreasonable to assume, therefore, that the small but statistically significant reduction in LESP observed during the luteal phase of the menstrual cycle in asymp-

tomatic women is only clinically important when it occurs in conjunction with one or more other factors that also reduce LESP or stress the competence of the LES. The combined effect of several such factors acting together presumably might reduce LESP enough to produce symptomatic heartburn in the luteal phase more frequently than in the follicular phase of susceptible women. Consistent with such a formulation is our unpublished observation that female medical students experience symptomatic heartburn more commonly during the latter half of their menstrual cycles (Days 15 to 28, i.e., luteal phase) than during the immediate postmenstrual period (follicular phase). Specifically, during the preceeding three years 25 female medical students at the University of Pittsburgh who were not using oral contraceptives agreed to keep a diary of their menstrual cycles and when they experienced symptomatic heartburn. As a result of such cooperation, we have been able to observe these women during a total of 405 complete menstrual cycles. Arbitrarily dividing each menstrual cycle into follicular phase (Days 1 to 14) and luteal phase (Days 14 to first day of vaginal bleeding) and then assigning each of the 135 documented episodes of heartburn to one or the other two menstrual cycle phases, we found a significant preponderance of symptomatic heartburn episodes during the luteal phase ($\psi^2 = 88.8889$; $p < 0.001$) as compared to the follicular phase. The failure to detect a significant difference in basal gastric pH and plasma gastrin levels during the course of this study as well as in previous studies[5, 6] tends to negate a role for either of these two factors in the genesis of the observed LESP reduction.

In summary, these studies demonstrate that: (1) Basal resting LESP during the luteal phase of the menstrual cycle is reduced in women relative to LESP measurements recorded in the follicular phase, and (2) changes in basal gastric pH and plasma gastrin levels cannot account for this observed decline in LESP during the luteal phase as compared to the follicular phase.

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Use of laparoscopy to determine the microbiologic etiology of acute salpingitis

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To determine the microbiologic etiology of acute salpingitis, laparoscopy was used in 26 patients to obtain specimens for a variety of microorganisms directly from the fallopian tube. Simultaneous culdocentesis was performed to obtain peritoneal fluid for microbiologic analysis. A variety of microorganisms were isolated from the fallopian tubes and cul-de-sac aspirate. However, the organisms isolated from the fallopian tube were not consistent with the cul-de-sac isolates. It appears that direct culture from the fallopian tube may be necessary to determine the microbiologic etiology and pathogenesis of acute salpingitis. *N. gonorrhoeae* was isolated from the cul-de-sac in 32 per cent of cases and the fallopian tube in 19 per cent. In patients with endocervical gonorrhea the gonococcus was isolated from the fallopian tube n 38.5 per cent of cases. Aerobic and/or anaerobic bacteria were present in the cul-de-sac aspirate in 46 per cent of patients and in the fallopian tube in 38 per cent. (AM. J. OBSTET. GYNECOL. 134:68, 1979.)

ACUTE SALPINGITIS remains a frequent disease in young women with significant implications for future fertility.[1–4] Concomitant with the current epidemic of sexually transmitted diseases[5] and increased usage of intrauterine contraceptive devices,[6, 7] the incidence of acute salpingitis has increased. It has been estimated that 500,000 to 700,000 women per year in the United States are treated for acute salpingitis.[7, 8]

The goals in management of acute salpingitis are prevention of infertility and the chronic residuals of infection, such as pelvic adhesions, hydro- or pyosalpinx, tuboovarian abscess, pelvic pain, and dyspareurnia, which often lead to surgical intervention.

To attain these goals, treatment regimens based on knowledge of the microbiologic etiology of acute salpingitis must be developed.

Until recently, the majority of attempts to determine the etiology of acute salpingitis have relied on isolation of microorganisms from the endocervix. With this methodology, acute salpingitis was divided into gonococcal and nongonococcal cases based solely on the presence or absence of *Neisseria gonorrhoeae* in the endocervix. However, recent investigations with culdocentesis and/or laparoscopy to obtain peritoneal fluid and tubal exudate have shown that the occurrence of pathogenic microorganisms in the cervix is not proof that such microorganisms are associated with tubal inflammatory disease.[3, 4, 9–13]

In an attempt to determine the microbiologic etiology of acute salpingitis, the present study utilizing laparoscopy to visually confirm the diagnosis and to obtain culture specimens directly from fallopian tube exudate was undertaken. Additionally, simultaneous culdocentesis was performed to determine the appropriateness of culdocentesis specimens in identifying pathogenic microorganisms involved in acute salpingitis.

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Material and methods

Study population. Women presenting to the San Francisco General Hospital Emergency Room with a diagnosis of acute salpingitis requiring hospitalization were entered into the study after appropriate informed consent was obtained. A tentative diagnosis of acute salpingitis was based on the following clinical criteria: (1) history of current lower abdominal pain, (2) presence of lower abdominal tenderness, (3) presence of cervical motion tenderness, (4) presence of adnexal tenderness, (5) oral temperature greater than 100.4° F., and/or (6) leukocytosis greater than 10,500 per cubic millimeter. At least four of these criteria had to be present for inclusion in the study.

Twenty-nine women were initially entered into the study. At the time of laparoscopy, the diagnosis of acute salpingitis was confirmed in 26 women. The remaining three patients (one case each of appendicitis, ectopic pregnancy, and bowel obstruction) were dropped from the study. Visual confirmation was based on the presence of: (1) purulent exudate from the fimbriated end or serosal surface of the fallopian tube, (2) erythema of fallopian tube, (3) edema and swelling of fallopian tube, and/or (4) inflammatory mass, such as pyosalpinx or tuboovarian abscess, involving the fallopian tube.

After the diagnosis of acute salpingitis was confirmed, microbiologic studies were performed on specimens from: (1) the endocervix, (2) exudate from the fallopian tube obtained at the time of laparoscopy, and (3) peritoneal fluid obtained via culdocentesis. The endocervix was cultured for *Neisseria gonorrhoeae, Chlamydia trachomatis,* Herpesvirus, *Mycoplasma hominis,* and *Ureaplasma urealyticum.* In addition to these microorganisms, specimens from the fallopian tube and culdocentesis fluid were cultured for aerobic and anaerobic bacterial.

Culture specimens for *N. gonorrhoeae* from the cervical os, culdocentesis, and laparoscopy were directly plated on NYC medium[14] and chocolate agar made with GC agar base, hemoglobin, and Isovitalex.* The plates were transported directly to the laboratory for incubation. Specimens from the endocervix, culdocentesis, and laparoscopy were cultured for *M. hominis* and *Ureaplasma urealyticum* by direct inoculation into NYC agar. A portion of the specimen was transported to the laboratory in mycoplasma A3X broth[15] and was inoculated into urea broth and A7 differential agar medium for mycoplasmas.[16, 17]

Culture specimens for chlamydia were put into Eagle's minimum essential medium and refrigerated at 4° C. when the specimen was not processed immediately. Iododeoxyuridine-treated monolayers of McCoy cells were inoculated with the specimen by centrifugation; the culture medium was replaced, and the cells were cultured 65 hours. The cells were examined with iodine and Giemsa stains for typical chlamydial inclusions.[18]

Culture specimens for herpesvirus were put into the same supplemented Eagle's minimum essential medium described for chlamydia. Monolayers of Vero kidney cells were inoculated with the specimen in the above medium and incubated.[18, 19]

Specimens for aerobic and anaerobic bacteria were freed of air bubbles and injected into anaerobic collection tubes containing oxygen-free carbon dioxide and rezazurin indicator. The specimens were taken directly to the laboratory by a member of the surgical team for immediate processing. The anaerobic cultures were set up in an anaerobic glove box. The following media were inoculated for cultivation of anaerobic bacteria: (1) Brucella agar medium* with 5 per cent defibrinated sheep blood, 100 μg per milliliter of vitamin K, and 5 μg of hemin; (2) the same supplemented agar medium containing 10 μg per milliliter of kanamycin; (3) thioglycollate 135C† supplemented as above with vitamin K and hemin; (4) prereduced, anaerobically sterilized chopped meat medium. Aerobic bacteria were cultured on trypticase soy agar with 5 per cent defibrinated sheep blood and MacConkey's agar.† Media were incubated at 35° C.

When there was insufficient exudate for direct aspiration, sterile, expandable plastic sponges‡ were introduced through the laparoscope and allowed to expand with fluid. The sponges were then placed into a 2.5 ml. dilution blank of prereduced, anaerobically sterilized

Table I. Distribution of microorganisms isolated from culture sites in cases of salpingitis (N = 26)

Microorganism	*Fallopian tube*	*Cul-de-sac*	*Endocervix*
N. gonorrhoeae only	4	4	1
N. gonorrhoeae + other microorganisms	1	4	12
Aerobic bacteria only (not gonococcus)	4	4	–
Anaerobic bacteria only	1	1	–
Mixed aerobic and anaerobic bacteria (not gonococcus)	4	3	–
Mycoplasma species only	1	2	9
Mycoplasma species plus other microorganisms	0	3	10
Chlamydia trachomatis	0	0	2

*Baltimore Biological Laboratory, Cockeysville, Maryland.

*Pfizer Lab., New York, New York.
†Baltimore Biological Laboratory.
‡Weck, Raleigh, North Carolina.

Table II. Relationship of endocervical, culdocentesis, and Fallopian tube culture results

Microorganism	Patients with endocervical isolation	Patients* with cul-de-sac isolation		Patients with Fallopian tube isolation	
		No.	%	No.	%
N. gonorrhoeae	13	8	61	5	38.5
M. hominis	19	1	5	0	–
Ureaplasma urealyticum	14	4	29	1	7

*Recorded as per cent of patients with positive endocervical cultures.

peptone yeast extract broth.[20] This volume was then divided and distributed into the various transport media.

Results

The age range in the study patients was 18 to 35 years, with a mean age of 24. There were 14 white, 10 black, and 2 Latin American patients included in the study. Seventeen patients (65.5 per cent) reported having been pregnant at least once and 14 patients were para 1 or greater. This was the initial episode of salpingitis in seven (27 per cent) women and the third or more episode in nine (34.5 per cent) patients.

In Table I, the general distribution of microorganisms isolated from the various culture sites is portrayed. Although *N. gonorrhoeae* was isolated from the endocervix in 13 (50 per cent) of the study group, it was isolated from the culdocentesis specimen in only eight (31 per cent) patients and from the fallopian tube in five (19 per cent). *N. gonorrhoeae* was the sole isolate from the endocervix of one patient, the culdocentesis aspirate in four patients, and the fallopian tube in four. In none of the patients without *N. gonorrhoeae* detected in the endocervix was this organism present in the fallopian tube or culdocentesis aspirate. In the 13 patients with *N. gonorrhoeae* isolated from the endocervix (Table II), the gonococcus was isolated from the culdocentesis aspirate in eight (61 per cent) patients, and from the fallopian tube in five (38.5 per cent).

Genital mycoplasma strains were frequently isolated from the endocervix of these salpingitis patients. *M. hominis* was isolated from the endocervix in 19 cases and *Ureaplasma urealyticum* in 14 cases. In nine (35 per cent) instances, mycoplasma strains were the sole isolate from the endocervix (Table I). Despite such frequent presence in the endocervix, mycoplasma strains were relatively infrequent isolates from the upper genital tract (Table II). *M. hominis* was isolated from the culdocentesis aspirate in one patient and from the fallopian tube in none of the cases. *Ureaplasma urealyticum* was found in the culdocentesis aspirate of four and in the fallopian tube of a single case. However, *ureaplasma urealyticum* was the sole isolate from the fallopian tube in only one patient and from the culdocentesis aspirates in two of 26 patients. *M. hominis* was never the sole isolate from the fallopian tube or culdocentesis aspirate. *C. trachomatis* was isolated from the endocervix in two patients. *C. trachomatis* was not isolated from the culdocentesis aspirate and/or the fallopian tube in any cases (Table I). However, 18 (69 per cent) of patients had a positive serologic titer against *C. trachomatis*. Herpesvirus hominis was not isolated from the endocervix, culdocentesis aspirate, or fallopian tube in any patients.

Aerobic bacteria as the sole isolates were found in the fallopian tube of four patients and in the culdocentesis aspirate of four patients (Table I). Anaerobic bacteria were the sole isolates from the fallopian tube in one case and the culdocentesis aspirate in one case. Mixed aerobic and anaerobic bacteria were identified in the fallopian tube in four cases and the culdocentesis aspirate in three cases. Mixed aerobic and anaerobic bacteria in association with *N. gonorrhoeae* were isolated from the fallopian tube in one patient and the culdocentesis aspirate in four patients. Over all, anaerobic bacteria were isolated from the fallopian tube in six (23 per cent) patients and from the culdocentesis aspirate in seven (27 per cent) patients. Aerobic bacteria (with or without *N. gonorrhoeae*) were isolated from the fallopian tube in nine (34.5 per cent) patients and the culdocentesis aspirate in 10 (38.5 per cent).

The bacterial isolates (not gonococcus) obtained from the fallopian tube and/or culdocentesis aspirate are listed in Table III. *E. coli*, Group B beta-hemolytic streptococcus, corynebacterium vaginale, alpha streptococcus, and *H. influenzae* were the most common aerobic isolates. Peptococcus, Peptostreptococcus, Bacteroides sp., and Clostridium were the most commonly isolated anaerobic organisms.

Comment

Classically, acute salpingitis has been divided into gonococcal and nongonococcal salpingitis. This classification has been based on the isolation of *N. gonorrhoeae* from the endocervix. The 50 per cent isolation rate for *N. gonorrhoeae* from the endocervix in this study is con-

sistent with previous investigations, in which isolation of *N. gonorrhoeae* from the endocervix was reported in 33 to 80 per cent of patients with acute salpingitis.[1, 4, 8, 10, 11, 13, 21, 22]

However, concern has been raised that the presence of pathogenic bacteria in the endocervix is not absolute proof that such bacteria are associated with upper genital tract infection. Many of the aerobic and anaerobic bacteria associated with pelvic infections reside in the cervix and vagina as part of the normal flora.[23] Utilization of culdocentesis, laparoscopy, and laparotomy to obtain culture specimens from peritoneal fluid and/or tubal exudate have shown an inconsistent and poor correlation between the cervical and intra-abdominal cultures. The recovery of *N. gonorrhoeae* from tubal exudate and/or peritoneal fluid in patients with acute salpingitis and endocervical gonorrhea has been reported in from 4 to 70 per cent of the patients.[9–11, 13, 24–28] In this study, we were able to isolate *N. gonorrhoeae* from the cul-de-sac aspirate in 61 per cent of the patients in whom *N. gonorrhoeae* had been cultured from the endocervix.

We were able to isolate *N. gonorrhoeae* from the fallopian tube in 19 per cent of patients with visually confirmed salpingitis. In patients with *N. gonorrhoeae* isolated from the endocervix, 38.5 per cent had *N. gonorrhoeae* isolated from fallopian tube exudate.

Like other investigators,[13, 28] we were able to frequently isolate *M. hominis* and *Ureaplasma urealyticum* from the endocervix. However, these studies reported a low (2 to 8 per cent) tubal isolation rate of genital mycoplasma; similarly, we were able to isolate *M. hominis* from the fallopian tube in none of our patients and *Urea-plasma urealyticum* in one of 14 patients with endocervical isolation of *Ureaplasma urealyticum*. Mardh and co-workers[12] were able to isolate *C. trachomatis* from the cervix in 19 of 53 patients (36 per cent) with acute salpingitis and from the fallopian tube in six of 20 tubal specimens obtained. Of the seven patients from whom *C. trachomatis* was isolated from the cervix and from whom tubal specimens were also obtained, *C. trachomatis* was recovered from the fallopian tube in six (86 per cent). In the present study, *C. trachomatis* was isolated from the endocervix in two of 26 patients; we were unable to isolate *C. trachomatis* from any of the Fallopian tube specimens. Although *C. trachomatis* has been implicated in Sweden[12] as a significant pathogen in salpingitis, its role in salpingitis in the United States awaits confirmation. In addition, the question of whether *C. trachomatis* is present as a colonizer or actually produces tissue destruction (alone or in synergy with other microorganisms) must be resolved.

Recent microbiologic investigations of peritoneal fluid obtained via culdocentesis in patients with salpingitis have disclosed the presence of a variety of aerobic and anaerobic bacteria (Tables IV and V).

Table III. Bacterial isolates (not *N. gonorrhoeae)* from the Fallopian tube and culdocentesis aspirate

Microorganisms	*Faliopian tube via laparoscopy*	*Culdocentesis aspirate*
Aerobic organisms		
Hemophilus influenzae	2	1
Hemophilus sp.	1	0
Alpha streptococcus	1	3
Corynebacterium vaginale	0	4
Enterococcus	0	1
Group B beta-hemolytic streptococcus	0	2
Escherichia coli	0	2
Proteus mirabilis	0	1
Lactobacillus	0	2
Anaerobic organisms		
Peptococcus	3	2
Peptostreptococcus	1	3
Bacteroides sp.	0	2
Bacteroidesoralis	0	1
Bacteroides melaninogenicus	0	1
Fusobacterium	0	2
Clostridium	0	3
Propionibacterium	0	2
Gaffkya	0	1
Ruminococcus	0	1

In the present study, *N. gonorrhoeae,* as the sole isolate or in combination with other microorganisms, was present in eight of 26 (31 per cent) patients. Aerobic and/or anaerobic bacteria were present in the culdocentesis aspirates of 12 (46 per cent) patients.

The assumption has been made[3, 9–11, 13] that bacteriologic evaluation of peritoneal fluid specimens obtained via culdocentesis is an accurate reflection of the microorganisms present in the fallopian tube of salpingitis patients. However, the discrepancies noted in Tables I, II, and III between culdocentesis isolates and fallopian tube isolates raises serious concern over such an assumption. The presence of aerobic and/or anaerobic bacteria (Table III) in the cul-de-sac specimens that were not isolated from the fallopian tube specimens requires further investigation to evaluate the reliability of culdocentesis as an appropriate method of specimen collection for determining the microbiologic etiology of acute salpingitis. One possible explanation for this discrepancy may be contamination of the culdocentesis aspirate with microorganisms from the vaginal flora. Another source for this difference might be that with pelvic peritonitis and an inflammatory reaction in the bowel wall the bowel wall defense mechanisms may be altered to allow diffusion of the bowel flora into the peritoneal cavity. It is also

Table IV. Bacterial isolation from culdocentesis aspirates in patients with acute salpingitis

Investigation	No. of patients with culdocentesis	No. of patients with endocervical N. gonorrhoeae		N. gonorrhoeae isolated from cul-de-sac		N. gonorrhoeae sole isolate from cul-de-sac		N. gonorrhoeae plus aerobic and/or anaerobic bacteria in cul-de-sac	
		No.	%	No.	%	No.	%	No.	%
Chow and colleagues[9]	20	13	65	1	5	Not stated		Not stated	
Eschenbach and associates[13]	54	21	39	7	13	6	11	1	2
Monif and associates[10]	17	16	94	11	65	5	29	6	35
Cunningham and co-workers[11]	76	45	59	22	29	10	13	12	16
Present study	26	13	50	8	31	4	15	4	15

Table V. Bacterial isolation from culdocentesis aspirates in patients with endocervical gonorrhea

Investigation	No. of patients with endocervical N. gonorrhoeae	N. gonorrhoeae isolated in cul-de-sac		N. gonorrhoeae sole isolate in cul-de-sac		N. gonorrhoeae plus aerobic and/or anaerobic bacteria	
		No.	%	No.	%	No.	%
Chow and colleagues[9]	13	1	8	Not stated		Not stated	
Eschenbach and associates[13]	21	7	33	6	28	1	5
Monif and associates[10]	16	10	62.5	5	31	5	31
Cunningham and co-workers[11]	45	22	49	10	22	12	27
Present study	13	8	61	4	31	4	31

possible that as we enter additional patients into our study culdocentesis specimens may be shown to reflect the microorganisms found in the fallopian tube specimens. Until further investigations to compare culdocentesis aspirates and direct fallopian tube specimens are performed, we believe that caution should be used in interpreting the bacteriologic results from specimens obtained by culdocentesis. If additional studies confirm the discrepancy noted in our investigation, then only specimens obtained directly from the fallopian tube will be appropriate to identify the microbiologic etiology of acute salpingitis.

Although the isolation of bacteria from the fallopian tubes and culdocentesis aspirates revealed significant differences, the fallopian tubes were also found to contain a variety of aerobic and anaerobic bacterial. In 10 of 26 patients with acute salpingitis (37.5 per cent), aerobic and/or anaerobic bacteria were isolated from the fallopian tubes.

The involvement of a mixed aerobic-anaerobic bacterial flora in salpingitis is similar to the pattern seen in patients with other types of pelvic infections.[23, 29, 30] In an experimental animal model, Weinstein and associates[31, 32] described a biphasic disease process for intra-abdominal infection. The initial phase was peritonitis and sepsis in which the major organisms involved were gram-negative faculatative aerobes, especially *E. coli*.

The second stage was intra-abdominal abscess formation in which the identified organisms were anaerobic bacteria. Their data suggested that to prevent both the peritonitis and abscess stages an antibiotic treatment regimen that covered the gram-negative aerobic and anaerobic bacteria was necessary. Whether this treatment approach is necessary in clinical situations is uncertain.

To achieve the preservation of fertility and to prevent the sequelae of acute salpingitis such as pyosalpinx, hydrosalpinx, tuboovarian abscess, dyspareunia, pelvic adhesions, and chronic pelvic pain, treatment regimens should be instituted that are based on a knowledge of the microorganisms involved in acute salpingitis. The initial step is to obtain specimens for microbiologic evaluation directly from the source of infection—the fallopian tubes. Then prospective, microbiologically controlled treatment regimens must be evaluated for short-term and long-term prognosis in patients with acute salpingitis. Many of the regimens currently used are based on the assumption that the gonococcus is the major etiologic agent in acute salpingitis. We believe that *N. gonorrhoeae* is an important

Aerobic bacteria only in cul-de-sac		*Anaerobic bacteria only in cul-de-sac*		*Mixed anaerobic/aerobic bacteria in cul-de-sac*	
No.	%	*No.*	%	*No.*	%
8	40	3	15	7	35
9	17	4	7.5	14	26
1	6	2	12	3	18
32 patients (42%) had aerobic and/or anaerobic bacteria other than *N. gonorrhoeae* isolated from the cul-de-sac					
4	15	1	4	3	12

Aerobic bacteria only in cul-de-sac		*Anaerobic bacteria only in cul-de-sac*		*Mixed aerobic/anaerobic bacteria in cul-de-sac*	
No.	%	*No.*	%	*No.*	%
Not stated		Not stated		Not stated	
2	9.5	0		3	14
1	6	2	13	3	18
12 patients (27%) had aerobic and/or anaerobic bacteria other than *N. gonorrhoeae* isolated from the cul-de-sac					
2	15	1	8	1	8

but not the only significant causative agent in the pathogenesis of acute salpingitis. Our study has confirmed the presence of a variety of microorganisms in the fallopian tube of patients with acute salpingitis. More commonly then the gonococcus, mixed aerobic-anaerobic bacteria have been isolated from the peritoneal fluid and/or fallopian tube exudate in patients with acute salpingitis. Rarely, genital tract mycoplasma have been identified in the fallopian tube or culdocentesis aspirates. It has been suggested that *C. trachomatis* is a major etiologic agent in acute salpingitis. We have not been able to confirm this finding, but further investigations are necessary to evaluate the possible role of *C. trachomatis* in the pathogenesis of acute salpingitis.

This study demonstrates that identification of gonococci in the endocervices of salpingitis patients does not prove that *N. gonorrhoeae* is present in upper genital tract disease. Utilization of Fallopian tube and peritoneal cultures has demonstrated that, in addition to the gonococcus, there is an involvement of a mixed aerobic-anaerobic flora in salpingitis patients that is similar to that seen in other female genital tract infections. In addition, mycoplasma infrequently may be present.

It has been suggested that the gonococcus may only be of importance to initiate the infection and to pave the way for other pathogenic bacteria from the cervical and vaginal flora to gain access to the upper genital tract.[9] Monif and colleagues[10] have postulated that there is an anaerobic superinfection with nonrecovery and probably elimination of *N. gonorrhoeae*. Lip and Burgoyne[27] noted that the isolation of *N. gonorrhoeae* was dependent on the stage of infection. They recovered the gonococcus from the cul-de-sac frequently within two days of the onset of salpingitis but infrequently if symptoms had been present greater than seven days. Their data support the idea of progression from gonococcal to mixed aerobic-anaerobic infection.

On the other hand, the failure to isolate *N. gonorrhoeae* in purulent exudate from the Fallopian tube or peritoneal fluid may be due to the ability of the gonococcus to attach to epithelial cells. Studdiford and colleagues[33] and Tronca and co-workers[34] were able to isolate *N. gonorrhoeae* from tissue but not the purulent exudate.

Our initial data suggest that caution be used in evaluating the use of culdocentesis to obtain culture material. Further studies must be done to either prove or disprove that culdocentesis aspirates reflect the microorganism mileau present in the Fallopian tubes of patients with acute salpingitis. Finally, long-term follow-up studies based on microbiologically controlled antibiotic treatment are necessary. We need to discover if a particular pathogen(s) carries(y) a worse prognosis for future fertility.

Whether treatment must provide coverage against *N. gonorrhoeae*, mixed aerobic-anaerobic bacteria, mycoplasma, and *C. trachomatis* is not clear at the present time. What appears clear is that eradication of the gonococcus may not be adequate treatment for patients with acute salpingitis. At the present time, we believe that doctors administering antibiotic treatment for patients with acute salpingitis should be cognizant of the polymicrobial nature of this infection.

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Psychological aspects of chronic pelvic pain in women

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Three psychometric tests: (1) A Dutch adjustment of the Minnesota Multiphasic Personality Inventory (MMPI), (2) The Amsterdam Biographical Questionnaire (ABV-V), and (3) The Interpersonal Relations Questionnaire (VIR) were administered to three groups of patients: (1) fifteen patients with chronic pelvic pain without clear organic cause; (2) twenty-two patients with chronic pelvic pain due to endometriosis; and (3) twenty-three pain-free patients. The analysis of the results showed that Groups 1 and 2 did not differ significantly on the MMPI and a global view of the two pain groups indicates a neurotic behavior, but both Groups 1 and 2 differed from Group 3 (the control group) and from Group 4 (the standardization group of the adapted MMPI). On the ABV-V the pain groups' answers were similar to those of neurotic patients, while the patient control group showed a certain neurotic tendency. The results on the VIR lead to the conclusion that Group 2 has the same profile as Group 1, although they did not deviate as strongly from the control group. As it is improbable that chronic pain for which an organic cause has been found occurs predominantly in patients with neurotic personality structure or neurotic reactions, we must admit that chronic pain with an organic origin can lead to neurotic reactions. These data confirm earlier studies on neurologic patients and on patients with chronic low back pain. Because even the patient control group showed a certain neurotic tendency, it follows that every contact with the medical world results in some degree of uncertainty and that the selection of control groups, when psychosomatic problems are being studied, is especially difficult. (AM. J. OBSTET. GYNECOL. 134:75, 1979.)

AMONG WOMEN who complain of chronic gynecologic pain are a significant percentage in whom the complaints have no clear organic basis. This problem is well known in gynecologic practice; in the gynecologic literature it has been called by many diverse names, and Naujoks, years ago, was already speaking of "die Krankheit mit den zwanzig Nahmen," the disease with 20 different names. Under these circumstances it seems logical to attempt to ascertain whether psychogenic factors contribute to either the origin or the maintenance of this condition.

In two recent studies concerning patients with chronic pelvic pain,[1, 2] the presence or absence of organic lesions of the internal genitals was ascertained and subsequent psychometric parameters were used to make a psychological evaluation of the patients. These parameters were also used to evaluate a control group of patients without pain. Castelnuovo and Krout[1] found a clear heightening of the hypochondriasis (HS), depression (D), and hysteria (Hy) scales of the MMPI for the patients with chronic pain. However, they also found heightened scores for the control patients. However, this study is not very informative concerning chronic pain without clear pathology, because patients with this sort of pain were not separated from those with pain of organic origin. It is also regrettable that no tests were carried out to see if there were significant differences between the groups with or without pain on the several distinct variables.

Beard and associates,[2] on the other hand, divided the patients into groups with or without probable organic cause for their pain and also included a control group. Neither the nature of the control group nor the duration of the complaint of pain was disclosed. With the

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Eysenck Personality Inventory (EPI) a significant difference was found on the neuroticism (N) score between the control group and the pain group without probable organic cause. The mean N score for patients with pain and organic pathology fell between that of the laparoscopy-negative patients with pain and the control group, differing with neither significantly. The extraversion (E) scores did not show significant differences between groups. With the Middlesex Hospital Questionnaire, which tapped principally neurotic symptoms and syndromes, Beard and colleagues[2] found no significant differences among their three groups.

Woodforde and Merskey,[3] by using the Middlesex Hospital Questionnaire and the Eyseck Personality Inventory, studied a group of patients with chronic pain of a physical (neurologic) origin in comparison with a group of patients in whom the chronic pain seemed to have a psychogenic origin. Sternbach and associates,[4] using the MMPI, compared patients complaining of chronic low-back pain with objective disorders with patients complaining of chronic low-back pain without clear organic disorders. Both of these authors reported no significant differences between these two experimental groups, which agrees with our findings.

Patient groups and methods

Renaer,[5] after a careful examination of 108 patients with chronic pelvic pain, diagnosed 28 of these cases as "chronic pain without obvious pathology." In 24 of those 28 cases a psychopathologic examination was conducted, unearthing in the course of one or more interviews, definite psychopathologic factors in 20 of them. It is difficult, however, to conduct these psychopathologic examinations in control cases; and even if this were done the results would not enable one to make statistical comparisons. Therefore a battery of psychometric tests was administered. These have the advantage of offering standardized results to which all subjects can be compared. At the same time the results of the psychological tests are amenable to statistical procedures and can be used to test certain hypotheses. Thus, psychometric tests were administered to three groups of patients: Group 1—fifteen patients with chronic pelvic pain without clear organic cause; Group 2—twenty-two patients with chronic pelvic pain and endometriosis, the chronic pain being most probably due to the endometriosis; and Group 3—twenty-three control patients.

The 15 patients with chronic pelvic pain without clear organic cause were patients who had for several months complained of pain. Most of them had been seen repeatedly at the gynecologic outpatient clinic, and all were subjected to a thorough examination, always including a laparoscopy, so that nongynecologic sources of pain could, with a high probability, be eliminated. In the 22 patients with chronic pelvic pain probably caused by endometriosis the presence of endometriosis lesions had been verified by laparoscopy, and the presumption that the pain was a consequence of the endometriosis lesions seems highly reasonable.

The 23 control subjects were patients who were admitted into the gynecologic clinic for benign nonpainful conditions that were not due to any psychogenic factors, e.g., patients with a benign tumor of the ovary found during a routine examination, a number of patients who underwent a curettage for intermenstrual bloodloss occurring either spontaneously or under ovulation inhibitors, or patients with a slight degree of bladder descent without urinary incontinence. In the selection of the control subjects, we attempted to find patients of about the same age, civil status, and educational level as the first two groups.

The psychological functioning of these three groups of patients was evaluated by the following psychological tests.

The Minnesota Multiphasic Personality Inventory. The Dutch adjustment by Nuttin and Beuten[6] of the MMPI of Hathaway and Kinley[7] was used. This gives the following list of clinical variables: HS = hypochondriasis, D = depression, Hy = hysteria, Pd = psychopathic deviation, Mf = masculinity/femininity, Pa = paranoia, Pt = psychasthenia, Sc = schizophrenia, Ma = hypomania, Si = social introversion. As validity scales to check the honesty of the answers the following were included: L = lie, F = validity, K = correction. At the end of the test were added: Es = ego-strength scale, R = repression scale, A = anxiety scale.[8, 9]

The Amsterdam Biographical Questionnaire. The ABV-V of Wilde[10] with four scales was also used: N = neurotic instability as manifested by the presence of psychoneurotic complaints, NS = neurotic instability as manifested by the presence of functional somatic complaints, E = social extraversion, and T = test-taking attitude.

Interpersonal Relations Questionnaire. The VIR questionnaire of Vertommen and Rochette[11] examines the male-female relationship. Our research concerned only the woman's view of her marriage. On both the reality and desired levels we examined how the wife felt about her husband (I → husband) and what the wife supposed that the husband felt about her (my husband → me). Eight content variables were measured: L = dominance, K = sociability, R = nurturance (tendency to offer help, support, and sympathy), B = dependence, S = abasement (a proneness to take blame, belittle oneself, and to apologize), Ve = detachment

Table I. Composition of the three groups

	Group 1 (N = 15)	*Group 2 (N = 22)*	*Group 3 (N = 23)*
Age: (yr.)			
<20	0	0	0
20-29	5	4	4
30-39	6	11	11
40-49	4	5	8
50+	0	2	0
Civil status:			
Married	13	21	22
Unmarried	2	1	0
Divorced	0	0	1
No. of children:			
None	7	11	4
1	2	4	8
2	3	3	6
3	1	2	2
4	2	2	3
Educational level:			
Grammar school	7	5	7
Junior high school	3	7	3
Senior high school	2	8	5
University	3	2	8

(aloof, withdrawn, and seclusive behavior), Vij = hostility, and A = autonomy.

The purpose of these various tests was to explore the psychological background of the three groups of patients and at the same time to make a quantitative addition to the above-mentioned psychopathologic evaluations.

The following hypotheses were tested: (1) The scores on the tested variables by women with chronic pelvic pain without a clear organic cause (Group 1) are significantly different from the scores of women whose chronic pain is most likely of organic origin (endometriosis, Group 2). (2) The scores of the women with chronic pelvic pain without clear organic origin (Group 1) differ significantly from those of the control group of women without pain complaints (Group 3). (3) The scores of the women with chronic pelvic pain of organic origin (endometriosis, Group 2) are significantly different from the control group of women with no pain complaints (Group 3).

A multivariate variance analysis was used to evaluate our findings, namely, the MANOVA computer program of Cooley and Lohnes.[12] This analysis compares the dispersions and centroids of the different groups. By rejecting the null hypothesis concerning the centroid equality one can, by means of the univariate F values, determine which of the test variables best differentiates between the various groups. Where appropriate, Student's t test was done for significance of difference.

When the results from the various groups were known, a comparison between the means of the standardization group of the test was also done. That standardization group is Group 4. For the comparisons which refer to Group 4 no multivariate test could be performed, as we do not possess the required detailed information. We thus tested the means by the Fischer's t test for uncorrelated means.[13]

Table II. Means and SDs on the MMPI for the various groups

	Group 1 (N = 15)		*Group 2 (N = 22)*		*Group 3 (N = 23)*	
Scales	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*
L	55.9	11.6	60.4	9.4	60.3	9.5
F	50.4	9.2	46.4	8.5	47.3	12.1
K	50.7	11.5	48.0	9.3	54.9	10.1
H	66.9	12.7	61.4	11.8	57.0	13.2
D	60.9	13.9	61.8	11.0	50.5	9.2
Hy	64.7	10.5	60.8	10.0	53.1	12.1
Pd	52.1	13.6	48.1	10.1	44.7	10.1
Mf	48.2	7.8	50.4	11.0	52.1	8.9
Pa	53.6	12.1	49.8	12.3	46.9	11.8
Pt	53.3	13.1	50.4	9.6	42.7	9.2
Sc	53.9	14.0	48.4	12.3	44.3	11.8
Ma	46.2	9.1	45.2	8.9	42.3	9.2
Si	53.1	12.6	51.1	8.3	44.3	10.1
Es	43.8	12.3	46.0	12.0	54.1	12.5
R	61.9	15.5	58.2	7.8	55.4	11.7
A	54.5	10.0	52.2	9.0	44.9	9.3

Results

The composition of the three groups regarding age, civil status, number of children, and the level of education is shown in Table I. The results for each psychological test will be discussed separately.

MMPI. In Table II we give the means and standard deviations in t scores for the various groups. For Group 4 the mean is 50 with a standard deviation of 10. Fig. 1 gives the graphic representation of the results, whereas the analysis of variance and t test are presented in Table III.

Multivariate variance analysis and t test on the results show that Groups 1 and 2 do not differ significantly on the clinical scales of the MMPI, while both Groups 1 and 2 do differ from Group 3 as well as from Group 4 (the standardization group). The two control groups (3 and 4) also appear to differ from each other.

Fig. 1 clearly shows similar profiles for Groups 1 and 2, the two pain groups. The inflated scores on hypochondriasis, depression, and hysteria clearly contrast with the two control groups, while the former groups (1 and 2) also display, when compared with Group 3, higher scores on psychasthenia (Pt), social inversion (Si), and anxiety (A), as well as lower scores on ego strength (Es).

A global view of the two pain groups (1 and 2) plainly indicates a neurotic behavior. The difference between

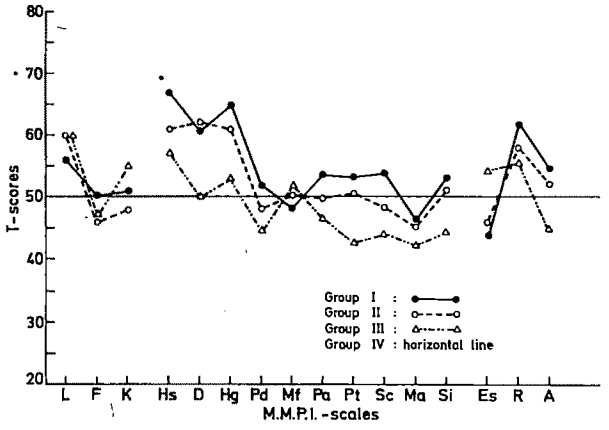


Fig. 1. Graphic presentation of the means of the different groups on the MMPI scales in t values. Abbreviations: *L* = lie, *F* = validity, *K* = correction, *Hs* = hypochondriasis, *D* = depression, *Hy*= hysteria, *Pd* = psychopathic deviation, *Mf* = masculinity/femininity, *Pa* = paranoia, *Pt*= psychastenia, *Sc* = schizophrenia, *Ma* = hypomania, *Si* = social introversion, *Es*=ego-strength scale, *R* = repression scale, *A* = anxiety scale.

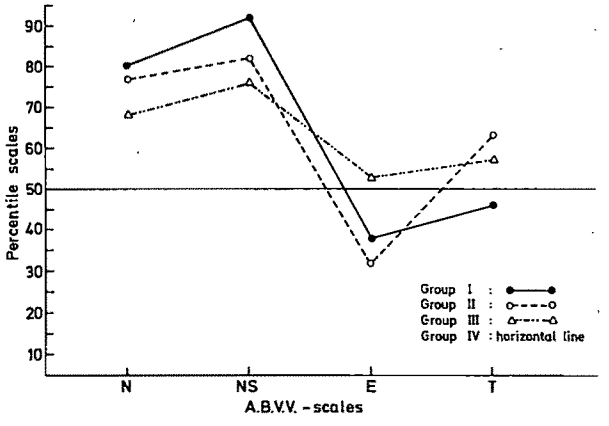


Fig. 2. Graphic presentation of the results of Table IV in percentile form. Abbreviations used: *N* = neurotic instability as manifested by the presence of psychoneurotic complaints, *NS* = neurotic instability as manifested by the presence of functional somatic complaints, *E* = social extraversion, *T* = test-taking attitude.

the two control groups lies principally in higher scores for the patient control group on hypochondriasis (Hs), psychopathic deviation (Pd), repression (R), and a lower score on anxiety (A) and on the scales that rather denote tendencies toward psychotic behavior.

ABV-V. In Table IV are given the means and standard deviations in raw scores and percentiles for the various groups; these results are expressed in percentile form in Fig. 2. As stated above, the comparison cannot include Group IV as the necessary data are not available.

From multivariate variance analysis on ABV-V for the different groups it appears that the two pain Groups 1 and 2 do not differ from each other on the ABV-V scales, and they do not differ from the patient control group. At an univariate level there is a significant difference between Group 1 and Group 3 on the NS scale. Patients with pelvic pain without clear organic cause display a stronger neurotic tendency manifested by functional somatic complaints, than the patient control group. (F = 6.73; this is significant at the 5% level).*

Fig. 2 clearly shows that the profiles from the two pain groups are very nearly parallel, although there is a tendency for Group 1 to be more neurotic and less defensive than Group 2. However, this difference is not a significant one. At the same time Fig. 2 shows that the patient control group differs from the norm group by a heightened neurotic tendency (N and NS). We were, however, not able to test this difference for significance.

Thus the results presented in this section are in the same direction as those of the MMPI, in that the two pain groups did not differ from each other significantly, while there is a difference between the two pain groups and the norm group. On the other hand in this test, a difference between the patient control group and the norm group is also indicated. Thus we can conclude that also on the ABV-V the pain groups answer as do neurotic patients, while the patient control group shows a certain neurotic tendency.

VIR. Space does not allow us to reproduce the means and standard deviation or the multivariate variance analysis and t test on the VIR for the different groups.† They show that Group 1 (pain without clear pathology) differs from Group 3 (patient control group) and Group 4 (norm group) concerning interpersonal functioning in marriage. The patients from Group 1 describe themselves as very unfriendly toward their husbands. On the other hand they wish very strongly that the marriage relationship would be characterized by the absence of detachment and suspicion. This interpersonal picture of the relationship indicates marriage conflicts which block positive emotional feelings toward the husband. On the other hand it appears from their wishes that they cannot tolerate any negative elements in their relationship, whether from their own side or especially from that of the husband.

Group 2 (pain and organic pathology) does not deviate significantly from Group 3 (patient control group) or from Group 1 concerning interpersonal functioning. Inspection of the results leads to the conclusion that to some degree Group 2 has the same profile as

*The results of the multivariate variance analysis will be sent on request.

†These data will be sent on request.

Table III. Multivariate variance analysis and t test on the MMPI for the different groups

Scales	*F ratios*			*t Ratios*		
	Groups 1-2	*Groups 1-3*	*Groups 2-3*	*Groups 1-4*	*Groups 2-4*	*Groups 3-4*
L	1.68	1.57	0.00	2.25*	4.81†	4.67†
F	1.88	0.70	0.08	0.15	1.69	1.22
K	0.64	1.33	5.42*	0.28	0.93	2.22*
Equality of dispersions	0.50	0.36	0.67			
Overall discriminations	3.67*	0.79	3.27*			
Hs	1.83	5.12*	1.33	6.48†	5.27†	2.42*
D	0.04	8.00†	14.36†	3.03†	5.44†	0.02
Hy	1.35	9.00†	5.14*	5.66†	4.99†	1.42
Pd	1.08	3.53	1.20	0.60	0.88	2.40*
Mf	0.47	1.87	0.30	0.69	0.21	0.97
Pa	0.88	2.81	0.65	1.38	0.08	1.42
Pt	0.61	8.04†	7.11*	0.96	0.17	3.31†
Sc	1.58	4.99*	1.29	1.08	0.72	2.58†
Ma	0.12	1.59	1.10	1.46	2.24*	3.50†
Si	0.35	5.35*	5.68*	1.17	0.49	2.57†
Es	0.31	6.03*	4.68*	2.37*	1.82	1.50
R	0.92	2.06	0.86	2.96†	3.83*	2.45†
A	0.52	8.72†	6.80*	1.72	1.01	2.31*
Equality of dispersions	1.37	1.63	1.17			
Overall discriminations	1.11	2.16*	3.54†			

Abbreviations: Hs = hypochondriasis, D = depression, Hy = hysteria, Pd = psychopathic deviation, Mf = masculinity/femininity, Pa = paranoia, Pt = psychasthenia, Sc = schizophrenia, Ma = hypomonia, Si = social introversion, Es = ego strength, R = repression, A = anxiety.

*Significant at the 5% level.

†Significant at the 1% level.

Table IV. Means, SDs, and percentiles on ABV-V for the different groups

Scales	*Group 1 (N = 15)*			*Group 2 (N = 22)*			*Group 3 (N = 23)*		
	Mean	*SD*	*Percentile*	*Mean*	*SD*	*Percentile*	*Mean*	*SD*	*Percentile*
N	76.8	28.7	80	73.8	22.7	77	64.4	2.36	68
NS	30.9	8.1	92	25.8	9.3	82	23.5	8.3	76
E	46.9	19.6	38	45.8	19.6	32	53.7	17.4	53
T	43.4	10.3	46	47.9	9.4	63	44.8	7.8	57

Group 1, although this group did not deviate so strongly from the control group.

One difference between the two pain groups can be seen if we compare them with the control group. Where the patients in Group 1 emphasized in their wishes that no negative feelings could be tolerated, Group 2 emphasized more the wish for greater dependence on each other within the relationship. In general we could remark that while Group 1 is fixated primarily on negative aspects that are to be avoided at any cost, Group 2 envisions a more positive relationship where each person can receive help and support from the other.

Comment

One may wonder why Group 1, the experimental group, comprised only 15 patients, whereas there were 22 in Group 2 and 23 in the patient control group. In fact it was our intention to administer the various tests to 28 patients with chronic pelvic pain without clear organic cause. Whereas the patients of groups 2 and 3 were very cooperative, several patients among the 28 of Group 1 were not, and only 15 completed the questionnaires. This leaves us with the interesting question of precisely why patients of this group showed this resistance to the psychological examination. It is possible that the patients who did not comply with our request had more psychological problems than those who completed the questionnaires.

Greater numbers, especially in Group 1 might have allowed us to find differences between more variables in the various groups than those uncovered by the statistical analysis, but this does not detract from the value of the present results. From these results it appears that our first hypothesis: "There is a significant difference between the variables concerning psychic functioning (as measured by our instruments) of patients with chronic pain but no clear organic cause and

those with chronic pain with an organic cause," must be rejected.

At this time it is difficult to accept the idea that chronic pain for which an organic cause has been found occurs predominantly in patients with neurotic personality structures or neurotic reactions. Therefore we must suppose the converse, that chronic pain with an organic origin can lead to neurotic reactions. This is indeed verified indirectly by the results of Sternbach and associates.[4] Using the MMPI, they compared patients with lower back pain of less than six months (acute) with patients whose lower back pain had endured more than six months (chronic). They found that the patients with acute lower back pain exhibited clearly milder neurotic symptoms than those with chronic back pain.

The question occurs also whether pain is more likely to become chronic in patients with previously existing neurotic personality structures. Research on this hypothesis would require further studies in which the personality structure before the onset of pain could in some way be measured. Surprisingly, when we examine the scores of our patient control group, we see that this group differs on several variables from the group on which the criteria were standardized.

Apparently Group 3 should be considered as a control group in a restrictive sense, i.e., in so far as these patients did not complain of pain; to obtain a truly good control group one must go outside the patient population. For this reason the scores of the three groups of our study were compared with the scores of the standardization group of the MMPI adapted by Nuttin and Beuten,[6] the ABV-B, and the VIR.

The comparison between Groups 1 and 4 shows more clearly that Group 1 exhibits a neurotic symptomatology, with heightened scores on hypochondriasis, depression, hysteria, and repression, and lower scores on ego strength (MMPI) and with heightened scores on neurotic instability (ABV-V).

Analogous results are found when Group 2 is compared with Group 4. The comparison between our patient control group (Group 3 and Group 4 is very interesting; we find in the patient control group a tendency toward high scores on hypochondriasis and on psychopathic deviation but, more strikingly, clearly lower scores on tests that indicate psychotic deviations: psychasthenia (Pt), schizophrenia (SC), hypomania (Ma), social introversion (Si); on the other hand there was an increase on repression (MMPI). On the VIR the patient control group presents a very idealistic view about their relationship with their husband. In the selection of the control group we felt that acceptable controls would be patients who were admitted to the clinic for symptoms or diseases that were not accompanied by pain, apparently had no psychogenic components, and were considered benign by the selecting gynecologist. Examples of these would be patients with slight blood loss between menstruations, either spontaneously or after taking the "pill," and patients with an incidentally discovered ovarian cyst or with descent of the bladder without urinary incontinence. The above-mentioned deviations of Group 3 from the norm Group 4 seem to indicate that the exposure to a clinical situation, even for symptoms whose nonmalignity is stressed by the doctor, but which nonetheless call for a surgical operation, promotes a person to "patient" status with the attending fear, uncertainty, and denial (MMPI). This may lead the patient to present an exaggeratedly idealistic image of herself (VIR). If we accept the idea that every contact with the medical world results in some degree of uncertainty, it follows that the selection of control groups when studying psychosomatic problems is especially delicate.

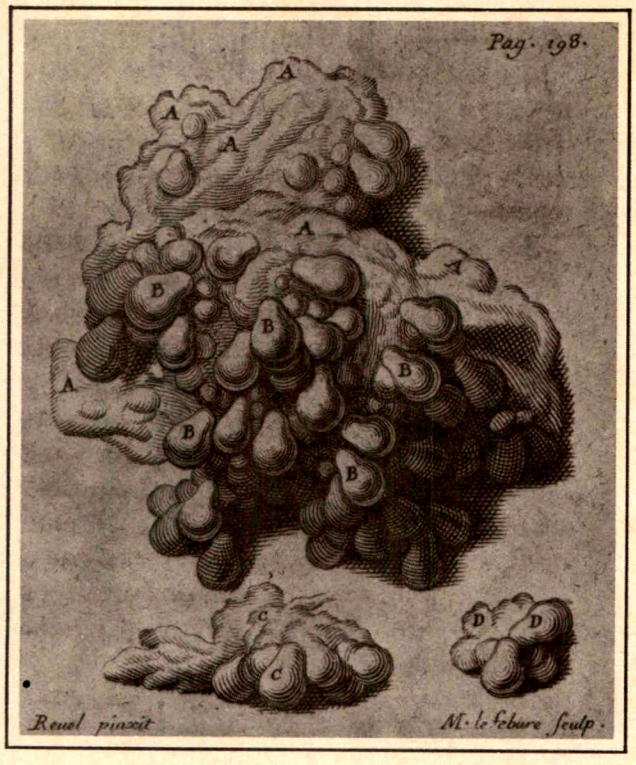
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Classic pages in
OBSTETRICS AND GYNECOLOGY
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La pratique des accouchemens soutenue d'un grand nombre d'observations . . .

PAUL PORTAL
Paris, Gabriel Martin, 1685



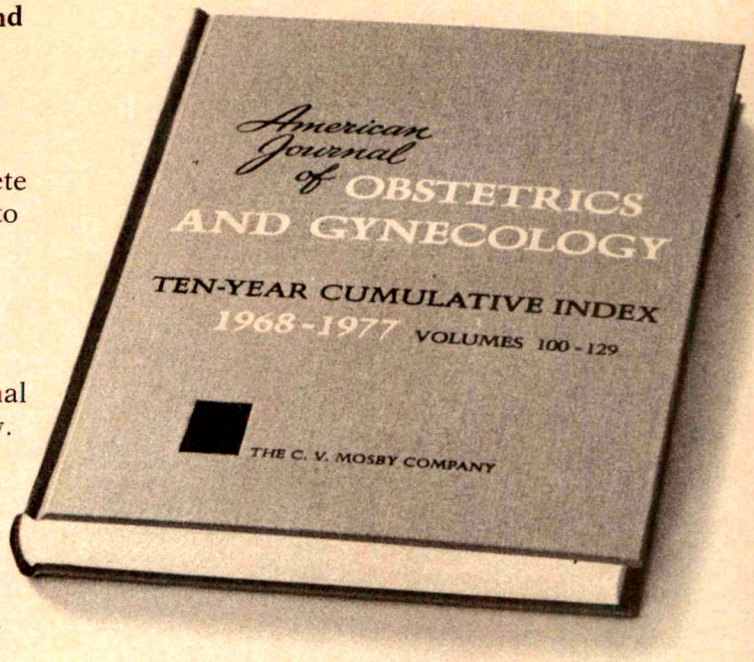
One of the major obstetric works of the late seventeenth century was that of Portal. A student of François Mauriceau and later a successor to him, and director of the obstetric service of the Hôtel Dieu, Portal based his treatise on clinical observations collected for more than 30 years. His 81 case reports possess a rare charm in their simplicity and clearness and reveal Portal's unique talents of observation. In the prefatory remarks he noted, "As I am ready to confess that my genius tends not in any wise to writing, so I hope the courteous reader will excuse the errors he may perhaps meet with in the following treatise, expecially since being sufficiently sensible, as well of my inability as the little inclination I had to publish these observations, the same would have laid concealed within the compass of my closet, had not some of my friends . . . persuaded and most urgently pressed me to oblige the world with what they were assured would tend to the instruction of those that profess midwifery . . .. I must intreat the reader, to have a regard not so much to the style and nicety of choice words . . . as the weight and truth of the matter itself . . .." Portal's chief contribution to the science of obstetrics lay in his clear recognition of placenta previa and its anatomy and clinical importance. Although previous writers, including those of the Hippocratic school and Ambroise Paré and Mauriceau, mentioned "flooding" preceding the delivery of the child (in fact, it was for this serious complication that Paré reintroduced podalic version), none of these authors recognized the true nature of this entity. In contrast, Portal not only reported eight cases in some detail (and alluded to six more) but also in these reports recognized that the placenta was attached over the lower uterine segment at or near the internal os. In addition, he detailed version and breech extraction and described how the placenta separates from the uterus. A typical "observation" (No. 69) was that of a patient who had bled for several days. On examination, Portal found the cervix well dilated. "I could put in three of my fingers foremost; I search'd with one finger first and found the afterbirth foremost, and closely joined around the inner orifice of the womb, which was the occasion of the excessive flux of blood; and as it had reduced the woman to a very low condition, so this joined to the other circumstances, made me fear the life both of the woman and child." After sending for a physician who prepared a prescription for the patient, Portal noted that the hemorrhage continued and he resolved to deliver her. He wrote: ". . . notwithstanding the great danger that must needs attend it . . . I found some means to convey my hand (well greased before)

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into the inner orifice of the womb, where I again felt the afterbirth fasten'd to it . . . I peel'd it off by degrees, and brought it out; and then turning my hand again in the womb, the first thing I met with, was the navel-string, along which I guided my hand first to the child's belly, and then downwards to the thigh, and thence lower to the leg and foot which I brought out and baptized . . .. Whilst I was pulling this foot the other followed, and the whole body after it." Portal noted that the child was alive and that the woman, who had been practically moribund, shortly recovered consciousness. Subsequently, the patient had a slow convalescence with an intermittent fever. In another case (No. 51), he explained the source of the bleeding and the circumstance of its production. He observed: "(I) found the afterbirth placed just before and quite across the whole inner orifice, which had actually been the occasion of the flux of blood: for, by the opening of the orifice, the said afterbirth then being loosened from that part where it adhered to before, and the vessels containing the blood torn and opened, produced this flooding, which sometimes is so excessive, as proves fatal to the woman, unless it be speedily prevented." It was not until a number of years later that P. Gottlieb Schacher demonstrated at autopsy that placenta previa was implanted over the lower uterine segment (De placentae uterinae morbis, Leipzig, 1709) and Edward Rigby first differentiated between placenta previa (unavoidable hemorrhage) and abruptio placentae (accidental hemorrhage) (Essay on Uterine Haemorrhage, London, 1775). Portal's treatise included his demonstration that podalic version could be performed with one foot, a procedure which, with Mauriceau and Jacques Guillemeau, he helped popularize after Paré. He also taught that face presentation usually ran a normal course and should be treated expectantly. In contrast to many of his contemporaries who practiced *accouchment forcé*, Portal advocated that dilatation of the cervix be left to nature. Although hydatidiform mole had been described previously, Portal published the first illustration of this condition (see figure) and the first detailed account of its removal by digital intrauterine manipulation (Observation No. 40). Portal wrote: ". . . I brought my finger (well greased with oil of sweet almonds) into the neck of the womb, and found the inner orifice much inflammed . . .. Advancing with my finger further into the womb, I felt a soft substance closely adhering to the inward orifice, which I supposing to be the afterbirth, I separated the adjoining parts from the orifice, without bruising it, when part of this soft spongy substance breaking off from the rest, I brought out a piece of the bigness of a walnut . . .. And the pains continuing, I pulled out a great part of this strange substance, which appeared full of fibers and white bladders full of water, glistering like crystal, and in shape not unlike our white currants. The quantity I brought forth weighed about two pounds . . .. Whilst my right hand was within the womb, I put the left to the woman's belly to push the womb downwards, which was of the bulk of a loaf of two or three pounds. The . . . figure [see illustration] represents a false conception, resembling in shape a bunch of currants, and in substance the seed of frogs." An English translation of Portal's treatise appeared in 1705 (The Compleat Practice of men and women midwives, or the true manner of assisting a woman in childbearing: illustrated with a considerable number of observations, London, H. Clark and J. Taylor).

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"I can't wait. I have to know if I'm pregnant."

*In an independent research laboratory setting, 90 samples were evaluated using Preg/Stat and Biocept-G (Wampole Laboratories, Cranberry, N.J.). All negatives were reassayed using a quantitative hCG-β subunit radioimmunoassay in order to rule out false negatives.

Of the 90 samples surveyed, there were 65 negatives by Preg/Stat, of which 63 were less than 5 mIU/ml as confirmed by the quantitative hCG-β assay. The two remaining samples were 9.0 and 9.6 mIU/ml respectively.

There were 25 positive results by Preg/Stat and quantitative hCG-β subunit RIA. However, only 22 of these results were confirmed positive by Biocept-G. The 3 samples ruled negative by Biocept-G and positive by the other two above-mentioned methodologies had values of 65.2, 181.4 and 65.7 mIU/ml hCG.

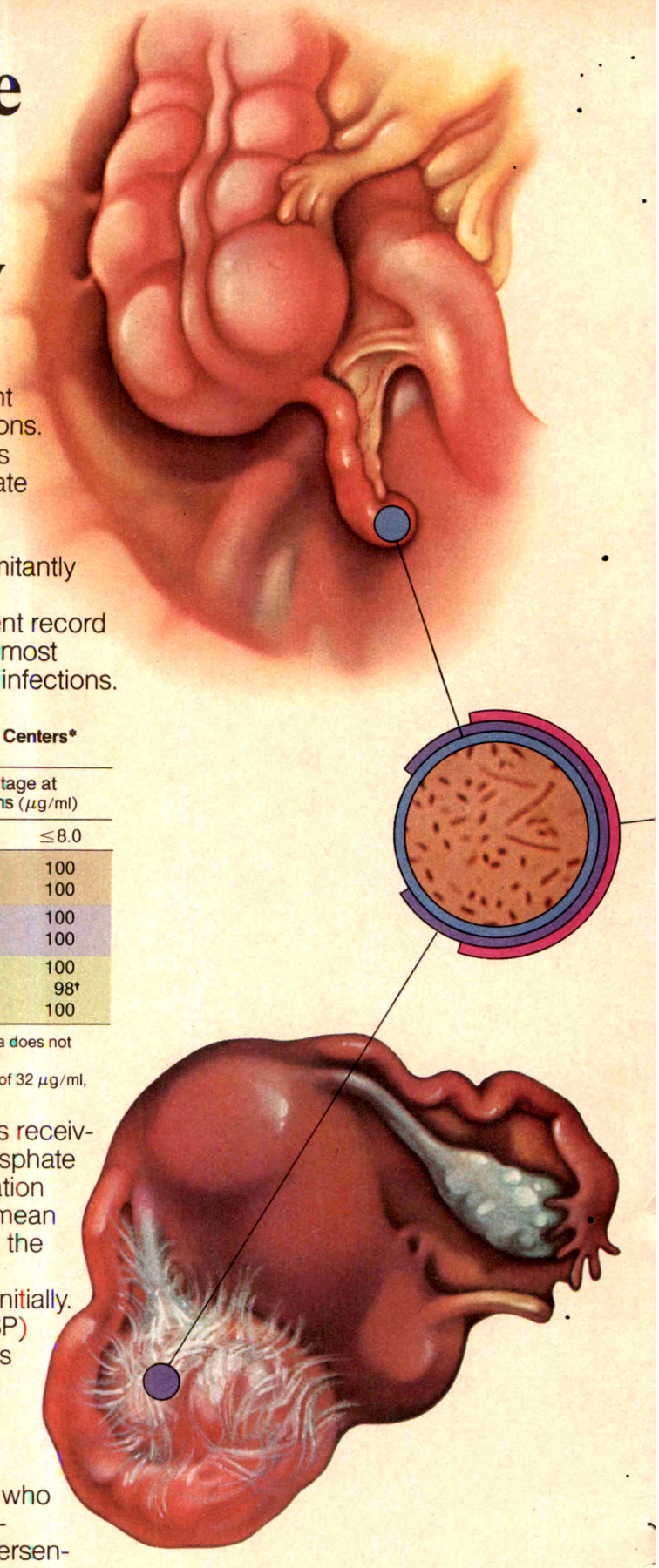
In this comparison, neither Preg/Stat nor Biocept-G produced false results within the respective methodology.

However, these results demonstrate that Preg/Stat is capable of detecting pregnancy earlier than Biocept-G.

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Clindamycin has maintained an excellent record of in vitro activity against *Bacteroides fragilis,* the most commonly isolated anaerobic pathogen in these infections.

In Vitro Susceptibility of *B. fragilis* at Three Infectious Disease Centers* as Determined by Agar or Broth Dilution Method

Center	Years	Number of Strains Tested	Cumulative Percentage at Various Concentrations (μg/ml)		
			≤2.0	≤4.0	≤8.0
Mayo	to 1972	195	96	100	100
	1974-76	92	93	100	100
Wadsworth	to 1972	123	89	96	100
	1972-75	76	84	96	100
Tufts	1973-76	26	100	100	100
	1977	59	98	98	98†
	1978	37	100	100	100

*Published data or data on file with The Upjohn Company. The use of this data does not constitute, imply, or suggest a recommendation of Cleocin by these centers.

†Of 678 strains tested at these centers, only one resistant strain, with an MIC of 32 μg/ml, was encountered.

In a study of six healthy male volunteers receiving 600 mg intravenous infusions of Cleocin Phosphate every six hours, the mean peak serum concentration following the fourth dose was 10.42 μg/ml. The mean serum concentration immediately before infusing the fourth dose was 3.27 μg/ml.

The parenteral route is recommended initially. Oral Cleocin® HCl (clindamycin HCl capsules, USP) may be instituted when the patient's clinical status has improved.

As there is no cross-allergenicity to the β-lactam antibiotics, such as the penicillins and cephalosporins, Cleocin is useful in seriously ill patients infected with susceptible organisms and who are sensitive to drugs in those classes. Hypersensitivity to clindamycin has been reported; if a hypersensitivity reaction occurs, the drug should be discontinued.

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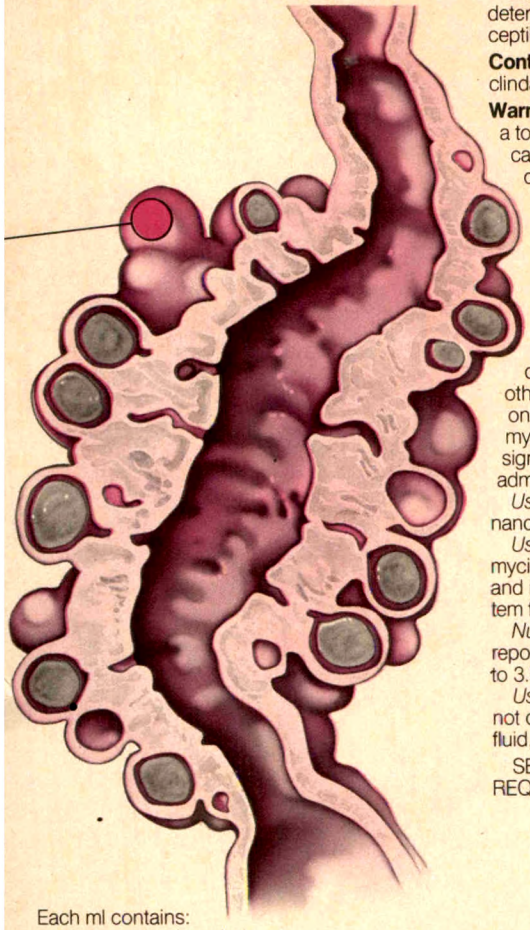
WARNING

Clindamycin therapy has been associated with severe colitis which may end fatally. Therefore, it should be reserved for serious infections where less-toxic antimicrobial agents are inappropriate, as described in the INDICATIONS section. It should not be used in patients with nonbacterial infections, such as most upper respiratory tract infections. Studies indicate a toxin(s) produced by *Clostridia* is one primary cause of antibiotic-associated colitis. See WARNINGS section. The colitis is usually characterized by severe, persistent diarrhea and severe abdominal cramps and may be associated with the passage of blood and mucus. Endoscopic examination may reveal pseudomembranous colitis.

When significant diarrhea occurs, the drug should be discontinued or, if necessary, continued only with close observation of the patient. Large-bowel endoscopy has been recommended.

Antiperistaltic agents such as opiates and diphenoxylate with atropine (Lomotil®) may prolong and/or worsen the condition.

Diarrhea, colitis, and pseudomembranous colitis have been observed to begin up to several weeks following cessation of therapy with clindamycin.



Each ml contains:
clindamycin phosphate equivalent to ..... 150 mg clindamycin
benzyl alcohol ..... 5 mg
disodium edetate ..... 0.5 mg
water for injection ..... qs
When necessary, pH adjusted with NaOH and/or HCl.

Indications: Clindamycin is indicated in the treatment of serious infections caused by susceptible anaerobic bacteria.

Clindamycin is also indicated in the treatment of serious infections due to susceptible strains of streptococci, pneumococci, and staphylococci. Its use should be reserved for penicillin-allergic patients or other patients for whom, in the judgment of the physician, a penicillin is inappropriate. Because of the risk of colitis, as described in the WARNING box, before selecting clindamycin the physician should consider the nature of the infection and the suitability of less-toxic alternatives (eg, erythromycin).

Anaerobes: Serious respiratory tract infections such as empyema, anaerobic pneumonitis and lung abscess; serious skin and soft-tissue infections; septicemia; intra-abdominal infections such as peritonitis and intra-abdominal abscess (typically resulting from anaerobic organisms resident in the normal gastrointestinal tract); infections of the female pelvis and genital tract such as endometritis, nongonococcal tubo-ovarian abscess, pelvic cellulitis and postsurgical vaginal-cuff infection.

Streptococci: Serious respiratory tract infections; serious skin and soft-tissue infections; septicemia.

Staphylococci: Serious respiratory tract infections; serious skin and soft-tissue infections; septicemia; acute hematogenous osteomyelitis.

Pneumococci: Serious respiratory tract infections.

Adjunctive Therapy: In the surgical treatment of chronic bone and joint infections due to susceptible organisms. Indicated surgical procedures should be performed in conjunction with antibiotic therapy.

Bacteriologic studies should be performed to determine the causative organisms and their susceptibility to clindamycin.

Contraindications: History of hypersensitivity to clindamycin or lincomycin.

Warnings: See WARNING box. Studies indicate a toxin(s) produced by *Clostridia* is one primary cause of antibiotic-associated colitis. Mild cases of colitis may respond to drug discontinuance alone. Moderate to severe cases should be managed promptly with fluid, electrolyte, and protein supplementation as indicated. Systemic corticoids and corticoid retention enemas may help relieve the colitis. Other causes of colitis should also be considered.

A careful inquiry should be made concerning previous sensitivities to drugs and other allergens. Antagonism has been demonstrated between clindamycin and erythromycin in vitro. Because of possible clinical significance, these two drugs should not be administered concurrently.

Usage in Pregnancy: Safety for use in pregnancy has not been established.

Usage in Newborns and Infants: When clindamycin phosphate is administered to newborns and infants, appropriate monitoring of organ system functions is desirable.

Nursing Mothers: Clindamycin has been reported to appear in breast milk in ranges of 0.7 to 3.8 μg/ml.

Usage in Meningitis: Since clindamycin does not diffuse adequately into the cerebrospinal fluid, the drug should not be used in meningitis.

SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN AND INTRAVENOUS CORTICOSTEROIDS SHOULD ALSO BE ADMINISTERED AS INDICATED.

Precautions: Review of experience to date suggests that a subgroup of older patients with associated severe illness may tolerate diarrhea less well. When clindamycin is indicated in these patients, they should be carefully monitored for change in bowel frequency. Prescribe with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Do not inject intravenously as an undiluted bolus; infuse as directed in package insert. Indicated surgical procedures should be performed in conjunction with therapy. Patients with very severe renal disease and/or very severe hepatic disease accompanied by severe metabolic aberrations should be dosed with caution and serum clindamycin levels monitored during high-dose therapy.

Prescribe with caution in atopic individuals. During prolonged therapy, periodic liver and kidney function tests and blood counts should be performed. Use may result in overgrowth of nonsusceptible organisms, particularly yeasts. Should superinfection occur, adjust therapy as clinical situation dictates. Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Use with caution in patients receiving such agents.

Adverse Reactions: *Gastrointestinal:* Abdominal pain, nausea, vomiting and diarrhea. (See WARNING box.) *Hypersensitivity Reactions:* Maculopapular rash and urticaria have been observed. Generalized mild to moderate morbilliform-like skin rashes are the most frequently reported of all adverse reactions. Rare instances of erythema multiforme, some resembling Stevens-Johnson syndrome, have been associated with clindamycin. A few cases of anaphylactoid reactions have been reported. If a hypersensitivity reaction occurs, the drug should be discontinued. The usual agents (epinephrine, corticosteroids, antihistamines) should be available for emergency treatment of serious reactions. *Liver:* Jaundice and abnormalities in liver function tests have been observed during clindamycin therapy. *Hematopoietic:* Neutropenia, eosinophilia, agranulocytosis and thrombocytopenia have been reported; no direct etiologic relationship to concurrent clindamycin therapy has been made. *Local Reactions:* Pain, induration, and sterile abscess have been reported after intramuscular injection, and thrombophlebitis after intravenous infusion. Reactions can be minimized or avoided by giving deep intramuscular injections and avoiding prolonged use of indwelling intravenous catheters. *Musculoskeletal:* Rare instances of polyarthritis have been reported.

How Supplied: Available as a sterile solution with each ml containing clindamycin phosphate equivalent to 150 mg clindamycin. Ampoules of 2 and 4 ml.

Caution: Federal law prohibits dispensing without prescription.

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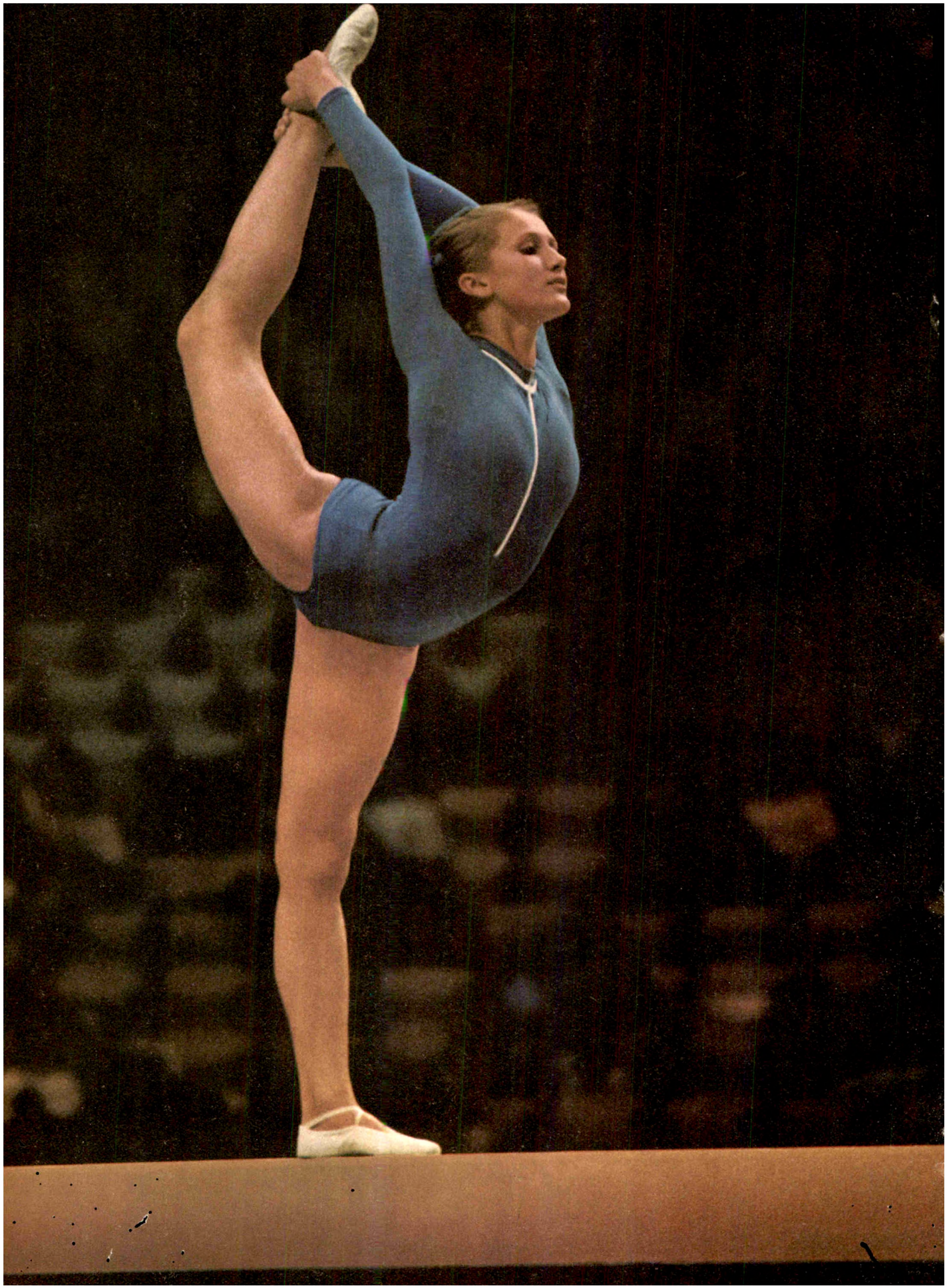
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With ModiCon, the majority of women who start with it stay with it.

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See the complete Prescribing Information for this product, a summary of which is on the next page.

ModiCon

†Serious as well as minor side effects have been reported with the use of oral contraceptives. These include thromboembolic disease. The physician should remain alert to the earliest manifestations of any symptoms of serious disease and discontinue oral contraceptive therapy when appropriate. The physician should be fully aware of the complete Prescribing Information for this product.

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IMPORTANT NOTE—This information is a BRIEF SUMMARY of the complete prescribing information provided with the product and therefore should not be used as the basis for prescribing the product. This summary was prepared by deleting from the complete prescribing information certain text, tables, and references. The physician should be thoroughly familiar with the complete prescribing information and patient information before prescribing the product.

INDICATION: CONTRACEPTION. The pregnancy rate in women using conventional combination oral contraceptives (containing 35 mcg or more of ethinyl estradiol or 50 mcg or more of mestranol) is generally reported as less than one pregnancy per 100 woman-years of use. Slightly higher rates (somewhat more than one pregnancy per 100 woman-years of use) are reported for some combination products containing 35 mcg or less of ethinyl estradiol, and rates on the order of three pregnancies per 100 woman-years are reported for the progestogen-only oral contraceptives. Table 1 gives ranges of pregnancy rates reported in the literature for other means of contraception. The efficacy of these means of contraception (except the IUD) depends upon the degree of adherence to the method.

Table 1: Pregnancies Per 100 Women-Years. IUD, less than 1-6; Diaphragm with spermicidal product (creams or jellies), 2-20; Condom, 3-36; Aerosol foams, 2-29; Jellies and creams, 4-36; Periodic abstinence (rhythm) all types, less than 1-47; 1. Calendar method, 14-47; 2. Temperature method, 1-20; 3. Temperature method—intercourse only in postovulatory phase, less than 1-7; 4. Mucus method, 1-25; No contraception, 60-80. **DOSE-RELATED RISK OF THROMBOEMBOLISM FROM ORAL CONTRACEPTIVES:** Two studies have shown a positive association between the dose of estrogens in oral contraceptives and the risk of thromboembolism. For this reason, it is prudent and in keeping with good principles of therapeutics to minimize exposure to estrogen. The oral contraceptive product prescribed for any given patient should be that product which contains the least amount of estrogen that is compatible with an acceptable pregnancy rate and patient acceptance. It is recommended that new acceptors of oral contraceptives be started on preparations containing .05 mg or less of estrogen. **CONTRAINDICATIONS:** Oral contraceptives should not be used in women with any of the following conditions: 1. Thrombophlebitis or thromboembolic disorders. 2. A past history of deep vein thrombophlebitis or thromboembolic disorders. 3. Cerebral vascular or coronary artery disease. 4. Known or suspected carcinoma of the breast. 5. Known or suspected estrogen-dependent neoplasia. 6. Undiagnosed, abnormal genital bleeding. 7. Known or suspected pregnancy (see WARNINGS, No. 5).

WARNINGS

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.
The use of oral contraceptives is associated with increased risk of several serious conditions including thromboembolism, stroke, myocardial infarction, hepatic adenoma, gallbladder disease, hypertension. Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks.

1. THROMBOEMBOLIC DISORDERS AND OTHER VASCULAR PROBLEMS. An increased risk of thromboembolic and thrombotic disease associated with the use of oral contraceptives is well established. Four principal studies in Great Britain and three in the United States have demonstrated an increased risk of fatal and nonfatal venous thromboembolism and stroke, both hemorrhagic and thrombotic. These studies estimate that users of oral contraceptives are 4 to 11 times more likely than nonusers to develop these diseases without evident cause. Overall excess mortality due to pulmonary embolism or stroke is on the order of 1.0 to 3.5 deaths annually per 100,000 users and increases with age. **CEREBROVASCULAR DISORDERS:** In a collaborative American study of cerebrovascular disorders in women with and without predisposing causes, it was estimated that the risk of hemorrhagic stroke was 2.0 times greater in users than in nonusers and the risk of thrombotic stroke was 4.0 to 9.5 times greater in users than in nonusers.
MYOCARDIAL INFARCTION: An increased risk of myocardial infarction associated with the use of oral contraceptives has been reported confirming a previously suspected association. These studies, conducted in the United Kingdom, found, as expected, that the greater the number of underlying risk factors for coronary artery disease (cigarette smoking, hypertension, hypercholesterolemia, obesity, diabetes, history of preeclamptic toxemia), the higher the risk of developing myocardial infarction, regardless of whether the patient was an oral contraceptive user or not. Oral contraceptives, however, were found to be a clear additional risk factor. The annual excess case rate (increased risk) of myocardial infarction (fatal and nonfatal) in oral contraceptive users was estimated to be approximately 7 cases per 100,000 women users in the 30-39 age group and 67 cases per 100,000 women users in the 40-44 age group. In terms of relative risk, it has been estimated that oral contraceptive users who do not smoke (smoking is considered a major predisposing condition to myocardial infarction) are about twice as likely to have a fatal myocardial infarction as nonusers who do not smoke. Oral contraceptive users who are also smokers have about a 5-fold increased risk of fatal infarction compared to users who do not smoke, but about a 10-to 12-fold increased risk compared to nonusers who do not smoke. Furthermore, the amount of smoking is also an important factor. In determining the importance of these relative risks, however, the baseline rates for various age groups must be given serious consideration. The importance of other predisposing conditions mentioned above in determining relative and absolute risks has not as yet been quantified; it is quite likely that the same synergistic action exists, but perhaps to a lesser extent. **Risk of Dose:** In an analysis of data derived from several national adverse reaction reporting systems, British investigators concluded that the risk of thromboembolism including coronary thrombosis is directly related to the dose of estrogen used in oral contraceptives. Preparations containing 100 mcg or more of estrogen were associated with a higher risk of thromboembolism than those containing 50-80 mcg of estrogen. Their analysis did suggest, however, that the quantity of estrogen may not be the sole factor involved. This finding has been confirmed in the United States. Careful epidemiological studies to determine the degree of thromboembolic risk associated with progestogen-only oral contraceptives have not been performed. Cases of thromboembolic disease have been reported in women using these products, and they should not be presumed to be free of excess risk. The risk of thromboembolic and thrombotic disorders, in both users and nonusers of oral contraceptives, increases with age. Oral contraceptives are, however, an independent risk factor for these events. **ESTIMATE OF EXCESS MORTALITY FROM CIRCULATORY DISEASES:** A large prospective study carried out in the United Kingdom estimated the mortality rate per 100,000 women per year from diseases of the circulatory system for users and nonusers of oral contraceptives according to age, smoking habits, and duration of use. The overall excess death rate annually from circulatory diseases for oral contraceptive users was estimated to be 20 per 100,000 (ages 15-34—5/100,000; ages 35-44—33/100,000; ages 45-49—140/100,000), the risk being concentrated in older women, in those with a long duration of use, and in cigarette smokers. It was not possible, however, to examine the interrelationships of age, smoking, and duration of use, nor to compare the effects of continuous versus intermittent use. Although the study showed a 10-fold increase in death due to circulatory diseases in users for five or more years, all of these deaths occurred in women 35 or older. Until larger numbers of women under 35 with continuous use for five or more years are available, it is not possible to assess the magnitude of the relative risk for this younger age group. This study reports that the increased risk of circulatory diseases may persist after the pill is discontinued. Another study published at the same time confirms a previously reported increase of mortality in pill users from cardiovascular disease. The available data from a variety of sources have been analyzed to estimate the risk of death associated with various methods of contraception. The estimates of risk of death for each method include the combined risk of the contraceptive method (e.g., thromboembolic and thrombotic disease in the case of oral contraceptives) plus the risk attributable to pregnancy or abortion in the event of method failure. This latter risk varies with the effectiveness of the contraceptive method. The findings of this analysis are shown in Figure 1 below. The study concluded that the mortality associated with all methods of birth control is low and below that associated with childbirth, with the exception of oral contraceptives in women over 40 who smoke. (The rates given for pill only/smokers for each age group are for smokers as a class. For "heavy" smokers [more than 15 cigarettes a day], the rates given would be about double; for "light" smokers [less than 15 cigarettes a day], about 50 percent.) The mortality associated with oral contraceptive use in nonsmokers over 40 is higher than with any other method of contraception in that age group. The lowest mortality is associated with the condom or diaphragm backed up by early abortion. The risk of thromboembolic and thrombotic disease associated with oral contraceptives increases with age after approximately age 30 and, for myocardial infarction, is further increased by hypertension, hypercholesterolemia, obesity, diabetes, or history of preeclamptic toxemia and especially by cigarette smoking. The risk of myocardial infarction in oral contraceptive users is substantially increased in women age 40 and over, especially those with other risk factors. The use of oral contraceptives in women in this age group is not recommended. Based on the data currently available, the following chart gives a gross estimate of the risk of death from circulatory disorders associated with the use of oral contraceptives:

SMOKING HABITS AND OTHER PREDISPOSING CONDITIONS—RISK ASSOCIATED WITH USE OF ORAL CONTRACEPTIVES

Age	Below 30	30-39	40+	
Heavy smokers	C	B	A	A—Use associated with very high risk.
Light smokers	D	C	B	B—Use associated with high risk.
Nonsmokers (no predisposing conditions)	D	C,D	C	C—Use associated with moderate risk.
Nonsmokers (other predisposing conditions)	C	C,B	B,A	D—Use associated with low risk.

The physician and the patient should be alert to the earliest manifestations of thromboembolic and thrombotic disorders (e.g., thrombophlebitis, pulmonary embolism, cerebrovascular insufficiency, coronary occlusion, retinal thrombosis, and mesenteric thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately. A four- to six-fold increased risk of postsurgery thromboembolic complications has been reported in oral contraceptive users. If feasible, oral contraceptives should be discontinued at least four weeks before surgery of a type associated with an increased risk of thromboembolism or prolonged immobilization. 2. OCULAR LESIONS. There have been reports of neuro-ocular lesions such as optic neuritis or retinal thrombosis associated with the use of oral contraceptives. Discontinue oral contraceptive medication if there is unexplained, sudden or gradual, partial or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal vascular lesions and institute appropriate diagnostic and therapeutic measures. 3. CARCINOMA. Long-term continuous administration of either natural or synthetic estrogen in certain animal species increases the frequency of carcinoma of the breast, cervix, vagina, and liver. Certain synthetic progestogens, none currently contained in oral contraceptives, have been noted to increase the incidence of mammary nodules, benign and malignant, in dogs. In humans, three case control studies have reported an increased risk of endometrial carcinoma associated with the prolonged use of exogenous estrogen in postmenopausal women. One publication reported on the first 21 cases submitted by physicians to a registry of cases of adenocarcinoma of the endometrium in women under 40 on oral contraceptives. Of the cases found in women without predisposing risk factors for adenocarcinoma of the endometrium (e.g., irregular bleeding at the time oral contraceptives were first given, polycystic ovaries), nearly all occurred in women who had used a sequential oral contraceptive. These products are no longer marketed. No evidence has been reported suggesting an increased risk of endometrial cancer in users of conventional combination or progestogen-only oral contraceptives. Several studies have found no increases in breast cancer in women taking oral contraceptives or estrogens. One study, however, while also noting no overall increased risk of breast cancer in women treated with oral contraceptives, found an excess risk in the subgroups of oral contraceptive users with documented benign breast disease. A reduced occurrence of benign breast tumors in users of oral contraceptives has been well-documented. In summary, there is at present no confirmed evidence from human studies of an increased risk of cancer associated with oral contraceptives. Close clinical surveillance of all women taking oral contraceptives is, nevertheless, essential. In all cases of undiagnosed persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be taken to rule out malignancy. Women with a strong family history of breast cancer or who develop breast nodules should be monitored with particular care if they elect to use oral contraceptives instead of other methods of contraception.

Figure 1. Estimated annual number of deaths associated with control of fertility and no control per 100,000 nonsterile women, by regimen of control and age of woman.

	15-19	20-24	25-29	30-34	35-39	40-44
No method	5.5	5.2	7.1	14.0	19.3	21.9
Abortion only	2.3	2.5	2.5	5.2	9.8	6.6
Pill only-nonsmokers	1.3	1.4	1.4	2.2	4.5	3.1
Pill only-smokers	1.5	1.6	1.6	10.8	13.4	58.9
IUDs only	1.1	1.2	1.2	1.4	1.6	1.4
Traditional contraception only	1.1	1.4	1.9	3.7	4.7	4.0
Traditional contraception and abortion	0.3	0.4	0.4	0.8	1.4	0.8

4. HEPATIC TUMORS. Benign hepatic adenomas have been found to be associated with the use of oral contraceptives. One study showed that oral contraceptive formulations with high hormonal potency were associated with a higher risk than lower potency formulations. Although benign, hepatic adenomas may rupture and may cause death through intra-abdominal hemorrhage. This has been reported in short-term as well as long-term users of oral contraceptives. Two studies relate risk with duration of use of the contraceptive, the risk being much greater after four or more years of oral contraceptive use. While hepatic adenoma is a rare lesion, it should be considered in women presenting abdominal pain and tenderness, abdominal mass or shock. A few cases of hepatocellular carcinoma have been reported in women taking oral contraceptives. The relationship of these drugs to this type of malignancy is not known at this time. 5. USE IN OR IMMEDIATELY PRECEDING PREGNANCY, BIRTH DEFECTS IN OFFSPRING, AND MALIGNANCY IN FEMALE OFFSPRING. The use of female sex hormones—both estrogenic and progestational agents—during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a nonsteroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare. This risk has been estimated to be on the order of 1 to 4 in 1000 exposures. Although there is no evidence at the present time that oral contraceptives further enhance the risk of developing this type of malignancy, such patients should be monitored with particular care if they elect to use oral contraceptives instead of other methods of contraception. Furthermore, a high percentage of such exposed women (from 30 to 90%) have been found to have epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether this condition is a precursor of vaginal malignancy. Male children so exposed may develop abnormalities of the urogenital tract. Although similar data are not available with the use of other estrogens, it cannot be presumed that they would not induce similar changes. An increased risk of congenital anomalies, including heart defects and limb defects, has been reported with the use of sex hormones, including oral contraceptives, in pregnancy. One case control study has estimated a 4.7-fold increase in risk of limb-reduction defects in infants exposed in utero to sex hormones (oral contraceptives, hormonal withdrawal tests for pregnancy or attempted treatment for threatened abortion). Some of these exposures were very short and involved only a few days of treatment. The data suggest that the risk of limb-reduction defects in exposed fetuses is somewhat less than one in 1,000 live births. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well-controlled studies that progestogens are effective for these uses. There is some evidence that triploidy and possibly other types of polyploidy are increased among abortuses from women who become pregnant soon after ceasing oral contraceptives. Embryos with these anomalies are virtually always aborted spontaneously. Whether there is an overall increase in spontaneous abortion of pregnancies conceived soon after stopping oral contraceptives is unknown. Pregnancy should be ruled out before initiating or continuing the contraceptive regimen. Pregnancy should always be considered if withdrawal bleeding does not occur. If pregnancy is confirmed, the patient should be apprised of the potential risks to the fetus and the advisability of continuation of the pregnancy should be discussed in the light of these risks. It is also recommended that women who discontinue oral contraceptives with the intent of becoming pregnant use an alternate form of contraception for a period of time before attempting to conceive. Many clinicians recommend three months although no precise information is available on which to base this recommendation. The administration of progestogen-only or progestogen-estrogen combinations to induce withdrawal bleeding should not be used as a test of pregnancy. 6. GALLBLADDER DISEASE. Studies report an increased risk of surgically confirmed gallbladder disease in users of oral contraceptives and estrogens. In one study, an increased risk appeared after two years of use and doubled after four or five years of use. In one of the other studies, an increased risk was apparent between six and twelve months of use. 7. CARBOHYDRATE AND LIPID METABOLIC EFFECTS. A decrease in glucose tolerance has been observed in a significant percentage of patients on oral contraceptives. For this reason, prediabetic and diabetic patients should be carefully observed while receiving oral contraceptives. An increase in triglycerides and total phospholipids has been observed in patients receiving oral contraceptives. 8. ELEVATED BLOOD PRESSURE. An increase in blood pressure has been reported in patients receiving oral contraceptives. In some women hypertension may occur within a few months of beginning oral contraceptive use. In the first year of use, the prevalence of women with hypertension is low in users and may be no higher than that of a comparable group of nonusers. The prevalence in users increases, however, with longer exposure, and in the fifth year of use is two and a half to three times the reported prevalence in the first year. Age is also strongly correlated with the development of hypertension in oral contraceptive users. Women who previously have had hypertension during pregnancy may be more likely to develop elevation of blood pressure when given oral contraceptives. Hypertension that develops as a result of taking oral contraceptives usually returns to normal after discontinuing the drug. 9. HEADACHE. The onset or exacerbation of migraine or development of headache of a new pattern which is recurrent, persistent, or severe, requires discontinuation of oral contraceptives and evaluation of the cause. 10. BLEEDING IRREGULARITIES. Breakthrough bleeding, spotting, and amenorrhea are frequent reasons for patients discontinuing oral contraceptives. In breakthrough bleeding, as in all cases of irregular bleeding from the vagina, nonfunctional causes should be borne in mind. In undiagnosed persistent or recurrent abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy. If pathology has been excluded, time or a change to another formulation may solve the problem. Changing to an oral contraceptive with a higher estrogen content, while potentially useful in minimizing menstrual irregularity, should be done only if necessary since this may increase the risk of thromboembolic disease. Women with a past history of oligomenorrhea or secondary amenorrhea or young women without regular cycles may have a tendency to remain anovulatory or to become amenorrheic after discontinuation of oral contraceptives. Women with these preexisting problems should be advised of this possibility and encouraged to use other contraceptive methods. Postuse anovulation, possibly prolonged, may also occur in women without previous irregularities. 11. ECTOPIC PREGNANCY. Ectopic as well as intrauterine pregnancy may occur in contraceptive failures. 12. BREAST FEEDING. Oral contraceptives given in the postpartum period may interfere with lactation. There may be a decrease in the quantity and quality of the breast milk. Furthermore, a small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs. The effects, if any, on the breast-fed child have not been determined. If feasible, the use of oral contraceptives should be deferred until the infant has been weaned. **PRECAUTIONS: General:** 1. A complete medical and family history should be taken prior to the initiation of oral contraceptives. The pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen and pelvic organs, including Papanicolaou smear and relevant laboratory tests. As a general rule, oral contraceptives should not be prescribed for longer than one year without another physical examination being performed. 2. Under the influence of estrogen-progestogen preparations, preexisting uterine leiomyomata may increase in size. 3. Patients with a history of psychic depression should be carefully observed and the drug discontinued if depression recurs to a serious degree. Patients becoming significantly depressed while taking oral contraceptives should stop the medication and use an alternate method of contraception in an attempt to determine whether the symptom is drug-related. 4. Oral contraceptives may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention, such as convulsive disorders, migraine syndrome, asthma, or cardiac or renal insufficiency. 5. Patients with a past history of jaundice during pregnancy have an increased risk of recurrence of jaundice while receiving oral contraceptive therapy. If jaundice develops in any patient receiving such drugs, the medication should be discontinued. 6. Steroid hormones may be poorly metabolized in patients with impaired liver function and should be administered with caution in such patients. 7. Oral contraceptive users may have disturbances in normal tryptophan metabolism which may result in a relative pyridoxine deficiency. 8. Serum folate levels may be depressed by oral contraceptive therapy. Since the pregnant woman is predisposed to the development of folate deficiency and the incidence of folate deficiency increases with increasing gestation, it is possible that if a woman becomes pregnant shortly after stopping oral contraceptives, she may have a greater chance of developing folate deficiency and complications attributed to this deficiency. 9. The pathologist should be advised of oral contraceptive therapy when relevant specimens are submitted. 10. Certain endocrine and liver function tests and blood components may be affected by estrogen-containing oral contraceptives: a. Increased sulfobromophthalein retention. b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability. c. Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG, free T4 concentration is unaltered. d. Decreased pregnanediol excretion. e. Reduced response to metyrapone test. **INFORMATION FOR THE PATIENT: (See Patient Package Insert). DRUG INTERACTIONS:** Reduced efficacy and increased incidence of breakthrough bleeding have been associated with concomitant use of rifampin. A similar association has been suggested with barbiturates, phenylbutazone, phenytoin sodium, and ampicillin. **CARCINOGENESIS, PREGNANCY, NURSING MOTHERS: See CONTRAINDICATIONS and WARNINGS. ADVERSE REACTIONS:** An increased risk of the following serious adverse reactions has been associated with the use of oral contraceptives (see WARNINGS): Thrombophlebitis. Pulmonary embolism. Coronary thrombosis. Cerebral thrombosis. Cerebral hemorrhage. Hypertension. Gallbladder disease. Liver tumors. Congenital anomalies. There is evidence of an association between the following conditions and the use of oral contraceptives, although additional confirmatory studies are needed: Mesenteric thrombosis. Neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis. The following adverse reactions have been reported in patients receiving oral contraceptives and are believed to be drug-related: Nausea, usually the most common adverse reaction. Vomiting, occurs in approximately 10% or less of patients during the first cycle. Other reactions, as a general rule, are seen much less frequently or only occasionally. Gastrointestinal symptoms (such as abdominal cramps and bloating). Breakthrough bleeding. Spotting. Change in menstrual flow. Dysmenorrhea. Amenorrhea during and after treatment. Temporary infertility after discontinuance of treatment. Edema. Chloasma or melasma which may persist. Breast changes: tenderness, enlargement, and secretion. Change in weight (increase or decrease). Change in cervical erosion and cervical secretion. Possible diminution in lactation when given immediately postpartum. Cholestatic jaundice. Migraine. Increase in size of uterine leiomyomata. Rash (allergic). Mental depression. Reduced tolerance to carbohydrates. Vaginal candidiasis. Change in corneal curvature (steepening). Intolerance to contact lenses. The following adverse reactions have been reported in users of oral contraceptives, and the association has been neither confirmed nor refuted: Premenstrual-like syndrome. Cataracts. Changes in libido. Chorea. Changes in appetite. Cystitis-like syndrome. Headache. Nervousness. Dizziness. Hirsutism. Loss of scalp hair. Erythema multiforme. Erythema nodosum. Hemorrhagic eruption. Vaginitis. Porphyria. Impaired renal function. (ORTHO-NOVUM 1/50□21 and ORTHO-NOVUM 1/50□28 contain tartrazine. Allergic reactions have been reported with the ingestion of this dye in some patients.) **ACUTE OVERDOSE:** Serious ill effects have not been reported following acute ingestion of large doses of oral contraceptives by young children. Overdosage may cause nausea, and withdrawal bleeding may occur in females.

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CURRENT DEVELOPMENTS

Legal and social issues in medical genetics

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This paper was written for the purpose of providing the physician with a perspective of the conflicting scientific, individual, and societal interests which have been evoked by increasing medical and scientific innovation in the area of human genetic disease. In it the following subjects are considered: (1) obtaining genetic information by amniocentesis, by genetic counseling, and by screening; (2) disclosure of genetic data to the patient; (3) inclusion of genetic data on the medical record; (4) courses of action available to the individual after disclosure of genetic information, i.e., abortion, sterilization, etc.; (5) the state and involuntary sterilization; and (6) prohibitions on marriage. (AM. J. OBSTET. GYNECOL. 134:83, 1979.)

HUMAN GENETIC DISEASE is rapidly assuming recognition as a major component of the world health deficit. Recent technologic advances now include procedures for the detection of increasing numbers of mutant gene carrier states, genetic defects in unborn children, and formerly unnoticed genetic disease states prior to onset. The need of genetic counseling for prospective parents is assuming increasing importance, and recent indications of behavioral correlates of chromosomal anomalies, if confirmed, will have important social and legal implications.

Each advance in the area of genetic information and procedures raises questions about the rights and obligations of the affected person, his family, and those who counsel and treat him. The very newness of the aforementioned technology has created variable contexts for the balancing of competing and at times conflicting scientific, individual, and societal interests. Moreover, the law's historic and major concern with the balancing of competing interests and resolution of conflicts is highly relevant, and it is obvious that the physician will serve as the major pressure point. Thus, we have prepared this paper for the purpose of providing the practicing physician and other medical personnel with perspectives of a number of relevant social implications and questions associated with genetic disease.

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A brief review of basic genetics

Before the governing subjects of this paper are discussed, a short review of basic genetics is deemed to be in order.

It is now widely accepted that the basic morphology, physiology, and biochemistry of an individual are determined by hereditary factors, acting in a relatively specific environment. By the act of reproduction, individuals originate from other individuals similar to them. Inheritance is the transmission of genes, located linearly on 23 pairs of chromosomes, from parent to offspring. The individual members of each pair of

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chromosomes represent homologous types donated by the two parental gametes. Twenty-two pairs are autosomes that determine the majority of the characteristics of the new individual, while the primary function of one pair is the determination of the sex of the individual.

Every individual develops from a basic single cell (zygote) formed by the union of one sperm and one ovum and the subsequent division of this primordial cell into two genetically similar daughter cells which in turn divide repeatedly to eventually form a population of trillions of cells. Therefore, every cell in an individual is assumed to have a "normal" set of chromosomes unique to that individual and similar, in the majority of individuals, to all other members of the species. The genes situated linearly along the length of these chromosomes express their effects through the production of chemical substances which in turn control the essential metabolic cycles of the cell.

It is now possible to select a sample of cells from an individual and, through proper techniques, describe the chromosomal profile of that individual. The number and structure of the chromosomal pairs, i.e., the karyotype, may be different from what is considered "normal" by comparison with an established standard karyotype as determined from large numbers of individuals with no clinical signs of defect. For example in Down's syndrome, or mongolism, microphotography usually notes three Number 21 chromosomes instead of the usual pair. Chromosomal sex can also be determined by observation of the chromosomal pairs. In the female subject, the sex chromosome pair consists of two long, uniquely identifiable chromosomes called the X chromosomes. In the male subject the pair has one long X chromosome and a shorter Y chromosome (always donated by the father). Numerical aberrations of the sex chromosome pair are occasionally noted, e.g., the XYY syndrome in which the individual has two Y chromosomes or Klinefelter's syndrome wherein the karyotype is characterized by two X chromosomes and one Y chromosome.

Obtaining genetic data at amniocentesis performed by the physician

After conception, the growing fetus is surrounded in the uterus of the mother by a liquid known as amniotic fluid. Into this fluid the fetus desquamates cells, most of which are assumed to contain a chromosomal complement identical to that of all other fetal cells. In 1966, Riis and Fuchs utilized this assumption in their study of inherited disease. They called the technique for retrieving fetal cells from the amniotic sac "amniocentesis." To accomplish this, a needle was passed into the fetal sac and a small amount of amniotic fluid gently aspirated. This fluid contained cells desquamated by the fetus and by the inner amniotic membrane.

By careful analysis of the fetal karyotype (following tissue culture in vitro), it is possible to observe architectural or numeric abnormalities which are etiologically related to inherited or congenital anomalies such as Down's syndrome or the sex chromosome syndromes noted above or other deviant phenotypic-karyotypic correlations. Biochemical analyses of amniotic cells following tissue culture in vitro can also diagnose a variety of genetically determined diseases, for example, Pompe's disease (an excess of simple sugars in the cells of muscle and nervous tissue), Tay-Sach's disease (a disorder which has a uniquely high frequency among Ashkenazi Jews) which is characterized by progressive mental and physical deterioration in newborn infants, or Lesch-Nyhan syndrome (self-cannibalism). In all, at least 61 different biochemically based ailments of varied severity can now be detected, and the list is constantly growing.

Amniocentesis as well as its attendant procedures has been refined to the point where some practitioners no longer consider it to be an experimental technique demanding special and rigorous safeguards in its application. Currently, there are no statutes restricting its use where a mother wishes voluntarily to undergo the relatively simple procedure. Therefore, it is now regarded as one of the procedures in the health care–delivery system available to the physician. Like the negligent performance of other medical procedures, breach of a duty the physician owes to his patient, resulting in ascertainable damages, will cause the physician to be liable for malpractice.

One area of potential liability is in the selection of the patients upon whom to perform amniocentesis. Unlike other surgical procedures wherein the patient presents with a specific complaint amenable to x-ray and laboratory testing, amniocentesis elevates personal and family histories to a greater position of importance. Thus, a professional duty may be imposed upon the physician to question the patient in these two areas beyond the normal cursory investigation characterizing most work-ups.

Physicians writing in the field tend to agree that the procedure is solely for the woman with a "high-risk pregnancy." In other words, a woman who has a greater than average chance of delivering a genetically defective child. This group would include couples where one parent is a carrier of a deleterious dominant gene or chromosomal rearrangement. In cases where such chromosomal carrier states are defined, analysis of the amniotic fluid is performed to identify the pres-

ence or absence of genetic disease. The same is true in single gene carrier states when the pattern of mendelian segregation clearly defines elevated probability of an affected fetus. Most young fertile women are defined as low-risk mothers because population statistics clearly indicate that probabilities are high that the fetus will be normal and clearly outweigh the risks inherent in the performance of the procedure and the ascertainment of genetic disease in the fetus. Thus, the procedure is not medically indicated for the majority of the contributors of offspring to the population.

Selection of the proper patient is judgmental with the physician and may be called into question. In the litigative context a physician's judgment is compared to the so-called standard of care. The standard of good medical care is the skill and learning possessed by members of the profession in good standing. As noted, a physician's conduct in a particular situation is measured against what other physicians of the same school would have done in the same or similar circumstances.[1] In the area of amniocentesis the general tenor of the profession suggests the procedure only for the high-risk group. A physician who selects a low-risk woman for amniocentesis breaches his duty to provide his patient with good medical care, since he subjects an improperly selected patient to a procedure for which there is no medical indication. The patient in this case suffers monetary damage in paying for a superfluous procedure and/or may be injured physically, a topic to be discussed below.

After selection of the proper patient for the procedure, the next source of potential liability is failure to procure an informed consent. As in all informed consent situations the actual paper is not as important as the discussion of the procedure and the associated risks and consequences the written form is intended to document. The physician views the signed consent form as protection from liability for untoward results that can arise. Of greater import, however, the consent process, especially in this situation, should expose any misconceptions the would-be parents may have, not only about the actual procedure but also regarding the information the procedure can yield.[2] It is not enough for the physician to state the risks to mother and fetus of the procedure itself. Emotionally, the parents may view a negative chromosomal analysis as insurance that the fetus will be perfect, a view the physician, in his preamniocentesis discussion, must discount.[3]

MacIntyre,[4] in conjunction with attorneys representing his genetic research clinic, devised a consent form for amniocentesis which covers four main areas of possible misunderstanding and potential subsequent litigation. After a brief description of the actual procedure, the form states that there are no guarantees that: (1) amniocentesis will not damage mother or fetus, (2) the attempt to get fluid will be successful, (3) the attempt to get useable cultures will also be successful, and (4) the child born will be normal even if a genetically unbalanced karyotype is found. The signed consent form is intended to insulate the physician from liability for battery, an "unconsented to touching," as well as establish the range of disclosure. Whether or not Dr. MacIntyre's description of the procedure and four-phase discounting of guarantees of success will so insulate the practitioner will depend upon the actual discussion that took place and the theory under which the local court operates as to proof of actual full disclosure. Of course, the consent does not insulate the physician from liability for his own malpractice.

Based upon a survey of the medical literature the potential for malpractice is not remote. If the procedure is done at 12 to 15 weeks of pregnancy, the transvaginal approach—passing the needle through the vagina—is often used. Performance of the procedure in this manner leads to a risk of infection greater than that of the transabdominal approach. Furthermore, the puncture of the cervical wall can lead to permanent rupture of the membrane. After 15 weeks the transabdominal method—passing the needle through the abdomen—is used. The risks to the mother are lessened but, since the amniotic fluid is clear or yellow, it is possible that the bladder may be punctured, producing an aspirate of urine and thus an unsuccessful test.[5]

There are also possible complications during and after amniocentesis whenever the procedure is attempted. That no fluid can be aspirated may mean a failure to reach the amniotic sac or a needle stuck in the fetus. The aspirate may be bloody, meaning an intrauterine vessel has been punctured. Greenish fluid may indicate perforation of the small bowel of the mother. After the procedure is performed, spontaneous abortion may occur due to infection, a traumatic lesion of the uterus, or rupture of the membranes. Fetal death may occur due to puncture by the needle. Puncture of the intestine may lead to maternal peritonitis. Puncture of an intrauterine artery may lead to fetomaternal hemorrhage. In each of these cases where a causal link may be established between the negligent actions of the physician and the untoward effect, the physician has not attained the standard of good medical care. This breach can lead to unnecessary suffering by the patient and necessitate further medical treatment and hospitalization.

After the aspirate is collected it is sent to a laboratory equipped to perform the necessary analyses of the karyotype of the fetus. Failure to obtain only fetal cells

or improper methodology (e.g., a nonaseptic technique) can cause culture contamination, leading to erroneous diagnosis, or require reaspiration. Twinning can cause erroneous results and often, for reasons which are not made clear in the literature, the karyotypes of both parents are not structured, thereby creating a situation where the entire diagnosis rests upon the fetal karyotype. These possibilities, if detected, will make a second amniocentesis necessary. If discovered after the period in pregnancy when the information obtained by amniocentesis can be utilized, such errors of negligence may be actionable as a breach of the contract between the patient and her physician to do an adequate diagnostic test for which the patient has paid.

The above catalogue of errors, which may be due to negligence, is not intended to be a "chamber of horrors" for frightening the medical profession. Nevertheless, the legal implications are obvious when it is noted that, as in other areas of medical therapy, licensing laws have not restricted the use of amniocentesis to a particular group of physicians sufficiently experienced in performing the procedure. Nadler,[6] an eminent researcher in the field of amniocentesis, reported that 1,000 amniocentesis procedures had been done prior to the date of his article's publication in 1971, with no deaths or mobidity. He thus termed the procedure as one of low risk. It must be remembered, however, that these procedures were almost all done by leaders in the field. As the procedure becomes more widely accepted and is performed by more and more physicians the issue will arise whether the standard of care is that of the ordinary competent physician or obstetrician performing the procedure or that of the experts who pioneered the technique. Where the obstetrician or physician performs the procedure he should be held to the standard of care of a specialist with his superior knowledge of the area. This would infer a standard as high as that set by the experts. Where the family physician performs the procedure, he too should be held to just as high a standard since amniocentesis is currently a procedure relatively reserved to the specialist and it would be unfair to the patient to have a less than adequate test performed just because her physician has attempted a procedure arguably beyond his expertise but not beyond his license to practice.

The solution to the problem of keeping the procedure one of low risk, yet allowing increasing numbers of physicians to perform it, will be through the restriction of amniocentesis to the hospital setting and definition of it as part of the privileges of certain physicians such as obstetricians or perhaps even other practitioners evidencing the requisite skill and having access to adequate equipment, e.g., sonography. Furthermore, state statutes regulating the functions of laboratories may aid in assuring quality control and ensuring the production of meaningful tests from the aspirate these laboratories receive. As Nadler suggested, amniocentesis should be done solely by an experienced obstetrician and the fluid sent to a laboratory experienced in culturing amniotic fluid cells and performing the particular diagnostic tests. He[6] wrote: "Because of the risks involved and the consequences of the results (whether or not the physician should suggest the patient have an abortion), only people with a great deal of experience should undertake intrauterine diagnosis."

Obtaining genetic data by the genetic counselor's questioning of his clients

Amniocentesis is a relatively precise method for prenatal ascertainment of a limited number of genetic defects. However, because of the relatively narrow time frame in which it is useful, most genetic data accrue via the more established method of reviewing family histories and establishing pedigree charts.[7] However, two major weaknesses are constant concomitants of this method: First, accurate and detailed family histories are difficult to obtain in any extensive form and second, unlike amniocentesis, interpretation of the data elicited by interviewing is based more on abstract probabilities than on specific knowledge. As an example of this second weakness, the following findings in statistical genetic theory will be helpful. The risk of recurrence of diseases due to abnormal autosomal genes is usually of the order of 25% to 50% of the offspring.[8] The risk of chrmosomal disorders involving visible defects in chromosomes is usually less than 2%.[8] However, if a chromosomal defect is transmissible or if a parent is a carrier, the risk of producing a defective child can be of the order of 20% for each pregnancy.[9] Since the counselor must deal with probabilities of this magnitude, information communicated by these probabilities is often less than satisfactory.

The interviewer who is not a physician, or the particular patient's physician, may be legally precluded from gaining easy access to relevant information contained in hospital records or the records of other physicians, unless he himself obtains a release of information from the patient or from relatives whose medical data may also be highly relevant.[10] A thorough pedigree investigation of a family may be stymied by the privacy rights of individual family members. The law, as yet, does not require that a person make known the fact he harbors a deleterious gene.[10] Thus, the legal issues relating to the interviewer's seeking of information do not concern so much the liabilities he may incur

in gathering his data but the impact of personal liberties regarding privacy which may hinder his thorough search.

Obtaining genetic data by screening

Screening for genetic traits can be done at any time in life. Most often, however, it is advised that screening be done: (1) preconceptually, to check if prospective couples are carriers; (2) prenatally, by amniocentesis as discussed above; (3) at birth or during the elementary school years, so that decisions may be made early enough in life to be acted upon successfully.

Screening programs are often sanctioned by state legislatures. Some programs are on a voluntary basis. In Massachusetts the Public Health Department conducts the Massachusetts Metabolic Disorders Screening Program in cooperation with the Massachusetts General Hospital and the Harvard Medical School.[11] Subject to inclusion are all babies in the Commonwealth for which blood–filter paper specimens are sent to the State Public Health Laboratories from hospitals. When the infant is ready for discharge urine–filter paper kits are given, to be returned one month after birth. The program is voluntary but has very high popular acceptance. The advantages of this system are its ease of operation and the fact that a large data base is being established for future research. This program has apparently gone well since its inception in the obtainment of information pertaining to genetic defects of a biochemical nature. Whether it has made a significant impact upon changing the population's attitude toward voluntary eugenic controls is unclear.

Some state-sponsored screening programs are mandated by law. Among these programs which are primarily concerned with infants and schoolchildren are those designed to diagnose phenylketonuria or the mutant gene carrier state (Hb^AHb^S) of individuals with the so-called "sickle cell trait."

The most widespread mandatory genetic screening procedure is the test for phenylketonuria. The genomic abnormality in this disease entity is responsible for the deficient action of a catalytic enzyme which allows production of an excess of phenylalanine in the body. The buildup of phenylalanine, if unchecked by placing the child on a phenylalanine deprivation diet, often leads to severe mental retardation. As a result of this screening procedure and the use of dietary regimens, the number of retardates with phenylketonuria admitted to state hospitals has consistently diminished. At least one commentator feels the widespread use of phenylketonuria screening is a case of overreaction by state legislatures to what appeared to be an easily explainable phenomenon. Recent studies have disclosed individuals with apparently normal intellects and with blood phenylalanine levels very similar to those of phenylketonuria victims. Yet, these "normal subjects" are placed on the same rigid deprivation diet, the effects of which are not yet fully elucidated.[12]

New York State has recently initiated a screening program among schoolchildren for the purpose of defining individuals with sickle cell trait.[13] The homozygous genotype (Hb^SHb^S) that results in sickle cell anemia is undetectable by amniocentesis and is found primarily in black populations. Approximately one in 400 to 500 neonates is affected. One in 11 to 16 black individuals is a carrier (Hb^AHb^S). New York has devised an obligatory screening program but only for urban schoolchildren. Rural children are screened only at the discretion of the local school physician. Furthermore, due to home-rule legislation, large urban areas such as New York City, Buffalo, and Rochester are exempt from the state legislation. It should be noted that some states have placed sickle cell screening on a voluntary basis or have made it optional on the part of the school physician as part of his routine physical examinations.

Several states have mandatory premarital screening legislation. In California, testing for rubella is a prerequisite for obtaining a marriage license.[14] It is known that rubella contracted by the mother early in her pregnancy can have devastating effects upon the growing fetus. Rubella, however, can only be contracted once in life. The object of the screening program is to determine if a prospective bride has had rubella or whether she should be inoculated against it.

This may be another instance of overreaction by a legislature. The statute was enacted before clinics could be established to perform the tests upon the influx of prospective couples. This situation led the State Public Health Director to instruct all couples to seek court waivers of the test, thus flooding local judicial calendars. The problem has been quickly dealt with and clinics should be ready to meet the demands for tests sometime in the near future.

In 1972, New York enacted premarital screening legislation regarding sickle cell anemia. Screening here is mandatory for applicants for marriage licences who are not Caucasian, Indian, or Oriental.[15]

Professor Linus Pauling has suggested very extensive premarital screening. His proposed legislation would screen all people for heterozygosity for deleterious genes, i.e., all people with a defective gene in a masked recessive state. These people would somehow be conspicuously marked (Professor Pauling does not mention how) and prohibited for marrying another person in the heterozygous state for the same trait.[12] For

a discussion of whether Pauling's prohibition of marriage is possible under our present legal system, see the part of this paper dealing with the courses of action a state may take with the genetic data obtained. The screening provision may be workable, however, whether performed premaritally or at birth.

Screening programs may be subject to constitutional attack. The New York sickle cell screening program for schoolchildren will serve as a good example. Judicial review of this legislation could arise in the following manner. As presently enacted, all urban children are to be tested for the sickle cell trait. The statute does exempt certain children from the procedure but only on religious grounds. Assume that a white youngster whose religion does not forbid such screening refuses to undergo the test or his parents refuse to allow the test to be done on their child. Enforcement of the statute will depend upon its constitutional validity.

However well meaning the New York statute is, cautious drafting may be the cause of its invalidity. A screening program may be enacted under the plenary police power of a state to protect the health and safety of its citizens. A limitation upon the police power is stated in the equal protection clause of the fourteenth amendment of the Constitution. The courts have interpreted this clause as demanding that the state have rational purpose and criteria in establishing a classification of individuals upon whom to apply legal burdens not applicable to others similarly situated. With respect to the New York statute, is residence a reasonable criterion for determining whether or not a child shall be tested? Apparently, the object of the legislators in this case was to avoid racial classification, despite the fact that such a classification probably could evince a compelling state interest to aid blacks. Instead, the law makes the distinction between urban and nonurban schoolchildren for the screening of a noninfectious, inherited disease for which there is no known cure. As in the hypothetical case, it is possible that nonurban blacks may not be screened for the disadvantageous genotype, whereas the urban white youngster will be tested even though he has slight probability of expressing the trait.[16] His refusal may very well be judicially sustained. Despite the understandable caution with which the New York Legislature drafted the statute, the act establishes a bad precedent. In the future the possibility of other screening tests involving ethnic or racial groups is likely. It would seem, within limits, such legislation could withstand an equal protection attack yet still acknowledge a racial or ethnic basis.

Finally, Motulsky[17] has suggested viewing screening from a different angle, not as conceived in legislative enactment but as a component of good medical practice. He has suggested that premarital screening, at least, be made part of the duties of a physician in performing his premarital physical examination. It seems this could apply as well to other physical examinations or pediatric evaluations.

Summary of techniques

Genetic information may be obtained by the physician doing amniocentesis, by the genetic counselor in his questioning of his clients, or by government-sponsored screening programs. To each is attached a certain amount of legal risk. The physician may insulate himself from a suit in battery by obtaining the informed consent of his patient. He cannot, however, relieve himself of liability for his own negligent acts if they cause harm to the patient. Yet, if done properly, amniocentesis is a definitive method of obtaining precise genetic information.

The counselor does not subject himself to a risk of liability as high as that of the physician, yet the information he obtains may be clouded by faulty memories or stymied by recalcitrant sources.

Screening programs have inherent difficulties in that, if they are voluntary, their success in obtaining accurate data depends upon the extent of the popular acceptance of the program. If the screening program is compulsory, care must be taken to avoid possible constitutional attacks, for while the state may have a rational goal in mind in obtaining genetic data it must obtain such data by a reasonable mechanism.

Disclosure of genetic data to the patient

Genetic data about specific individuals may be obtained through amniocentesis, interviewing or screening. Once such data are collected, questions of what findings should be divulged and to whom naturally arise.

As a preliminary precondition for this discussion, the word "patient" must be defined. A patient is anyone who undergoes medical or surgical treatment. In the context of disclosing genetic information the patient is the person from whom data have been collected. Despite the fact that amniocentesis is done to gather data on a fetus, the patient in those cases is the pregnant woman. Finally, while there may arise a duty to disclose information to the parents of a newborn infant or older child, the youngster still remains the patient.

In a symposium held in 1969, in which leading clinical geneticists participated, the question of divulging information to patients, family, and attending physicians was raised.[18] The issue centered around the physician's primary duty to maintain the confidentiality of his relationship with his patient and the fact that, by its

very nature, genetic information often concerns existing relatives and may concern persons who may enter the family in the future.

The concensus was the rather bland statement that information should be disclosed to those who need to know if disclosure does not cause more harm than good. The inference to be made from the statement of the participants was that since disclosure of medical information can often affect the well-being of the patient, and since the law allows the medical profession to establish its own standard of care, this would appear to end the matter.[19] (It must be remembered also that at this juncture the subject is not the amount of disclosure necessary to obtain informed consent for the performance of a procedure, a subject discussed above.)

However, specific answers of the geneticists were quite illuminating. All seemed to agree that relatives could not be told findings related to a patient without the consent of the patient. But as to disclosure to the patient of his own genetic make-up, the physicians noted various areas of nondisclosure. One physician would only divulge information on traits which predispose the individual to biochemical disease and only if that disease could be avoided or ameliorated. Some felt that aberrations of the sex chromosome pair should not be divulged. Others would not divulge information currently thought to be of a psychiatric nature.

As an example of the latter two areas of nondisclosure, the XYY syndrome may be cited. An extended discussion of this genetic defect should give clues as to the reasons physicians are loath to divulge the findings. The XYY syndrome has recently gained much notoriety in the criminal law for its possible implications in a plea of insanity based upon an organic cause by a defendant to show his lack of capacity to form the requisite intent needed to be guilty of certain crimes. Perhaps the most famous case in which the plea was attempted was in the appeal of the murder conviction of Richard Speck who, in 1966, killed eight student nurses in Chicago. Tests done upon Speck "revealed" he had the XYY type of chromosomal complement.[20] Courts are not unanimous in allowing such a plea. In France the plea was allowed. In Australia it was not.[21]

In the mid-1960's Jacobs and associates[22] did a study on men in a maximum-security prison. Of the 315 men tested, nine were positive for the XYY aberration. In other words, whereas normal male subjects have a sex complement of one X chromosome from the mother and one Y chromosome from the father, these men had an extra "maleness" chromosome. Court-Brown and colleagues noted no physical characteristics different from those of other male subjects in these XYY individuals, except that they were taller. Prison records, however, disclosed that onset of criminal activity in these men commenced five years before the average, 90% of which was against property. Court-Brown and associates stated: "This picture strongly favors the idea that the additional Y chromosome genetically predisposes the 47,XYY male to the development of a psychopathic personality and to consequent aberrant behavior and antisocial conduct." However, no studies have shown a direct cause-and-effect relationship between the syndrome and predisposition to crime.

47,XYY fetuses can be discerned utilizing cultured amniotic fluid cells in vitro. The issue then is whether such information when discovered should be disclosed to the parents (perhaps coupled with a recommendation for abortion) or whether euthenic procedures should govern the child's subsequent development after birth in the same way the phenylalanine deprivation diet is suggested after the detection of phenylketonuria. In either case it is difficult on a practical basis to imagine a physician advising that the patient-mother undergo an abortion or that the patient-child be placed on a specific regimen without any explanation as to the reasons for his advice.

In addition to the comments elicited at the symposium most geneticists have been inclined to recommend that neither a child found to be 47,XYY nor his parents be informed of this finding and that no attempt be made to treat the child prophylactically to forestall the emergence of criminal tendencies. The reason for this attitude is based upon an analysis of the population used to detect the syndrome originally, i.e., prisoners. Detractors cite the prison population as being highly unrepresentative. They state that studies show that only 50% of serious crimes are ever reported to the police. Of these, only 12% result in arrest, of which only half of the arrestees are convicted and less than half of the latter number incarcerated.[23] However, specific surveys of 47,XYY children do show them to have a lower threshold for frustration, leading to more frequent tantrums, paroxysmal aggression, unsolicited rage, and, when older, sexual exoticism.[23]

For the physician, the duty he may feel to divulge information as to an XYY child presents a serious dilemma, at least morally, whether to his patient, the child, or the parents. The causal link between the aberration and propensity for crime has not yet been proved although there is some statistical evidence for its existence. The physician can decide not to divulge to the parents and run the risk of serious repercussions, since the child will not be placed in a euthenic environment in which an effort is made to spare the child familial instability, poor parental supervision, and other pressures with which his genetic make-up al-

legedly does not allow him to cope. At least ethically, the physician may be abdicating his duty to provide his patient, the child, with the best possible care. On the other hand, the physician can divulge this information and perhaps by doing so encourage the parents to establish a false and sterile environment for the child in which no natural aggressive behavior is tolerated, perhaps leading to psychological trauma to the youngster beyond that which his alleged XYY constitution would elicit.[23, 24] Disclosure would not be made to the child himself in any event. Physicians would undoubtedly assume such a subject is beyond the comprehension of the patient. More difficult decisions to disclose would naturally occur as the patient-child grew older.

Beyond the debate in the medical world regarding disclosure of findings related to sexual aberrations, some physicians are beginning to question the dissemination of any sex chromosome information. Such disclosures as the gender of a fetus as determined by amniocentesis are rarely crucial to the management of an obstetric case by the physician. In a letter to the *Journal of the American Medical Association,* a Utah pathologist related that a 38-year-old mother of one boy and two girls requested amniocentesis to rule out the possibility of Down's syndrome. The fetus, after testing, was reported to be genetically normal and female. Upon disclosure of this information the parents decided to obtain an abortion on the sole ground that they did not wish another girl. The physician felt that this was an improper use of the knowledge discernible by amniocentesis and therefore should not be divulged.[25]

Guidelines as to disclosure to the patient or relatives, as physicians view them, thus appear to be: (1) reveal to the patient, or his parents if a minor, only what he can grasp and what will not be psychologically damaging; (2) obtain the patient's consent to discuss the matter with the family; (3) encourage or require further genetic counseling for the patient after the information has been disclosed. The suggested guidelines as to disclosure to patient and family would appear to comport with typical duties of the physician to ensure the privacy of the patient. It is debatable whether judgments as to what information to withhold could stand judicial analysis when based upon a physician's perceived notion of the psychologically damaging nature of his disclosure.

As reflected by the comments elicited by the participants at the symposium, physicians appear to be laboring under the notion that disclosure problems should be resolved in favor of the foremost responsibility of a physician to his patient, i.e., doing what is best for the patient. They appear to believe that this may be discerned by what is considered good medical care as determined by the profession itself. This may be not the view of the public and the law.

Generally, the issue of disclosure arises in the litigative context in cases alleging failure of the physician to obtain informed consent for a procedure, thus rendering the physician liable in battery after the procedure has been accomplished with an untoward result. The patient argues that the freedom of choice was limited by the physician. In such a case, the patient asserts that he was denied the right to make an intelligent decision whether to consent or to refuse to undergo the procedure or to choose other possible options due to the physician's alleged omission to state all the pertinent facts regarding the intended treatment.[26]

In the case of *Nishi vs. Hartwell,* 473 p 2d 116 (Hawaii, 1970), a malpractice action was predicated on the fact a physician did not alert his patient to the collateral risks of an intended surgical procedure. The patient's widow argued that such an omission obviated the possibility of the patient's giving informed consent and thus rendered the physician liable in damages for battery after the operation had taken place. On appeal the physician prevailed. He argued in defense that disclosure of the collateral risks of the surgery would have caused the patient great apprehension and thus aggravated a pre-existing condition which the procedure was intended to diagnose prior to definitive surgical intervention. The court allowed the physician to introduce evidence as to the standard of care in the medical profession regarding disclosure in such a situation by his own testimony. This apparent infringement of the patient's freedom of choice by the physician represents a departure from the basic rule as cited above.

Whether courts will extend the physician's standard of care as the absolute criterion in situations not immediately involving the physical well-being of the patient is arguable. To explore this one must look at the two alternatives available to the physician regarding disclosure. What are the litigative possibilities if a physician does divulge genetic information to a patient or the parents in the case of an infant or fetus? Let us use the above-noted examples of findings of 47,XYY. To be liable in malpractice the physician must breach a duty to his patient, causing the patient harm and damages. The physician may well feel he has breached his duty to his patient for stating a fact that may be psychologically damaging. However, it is difficult to see the harm the patient has suffered. Perhaps the revelation will be startling but it is hard to conceive that stating a fact to a patient will be actionable as the infliction of emotional distress, for instance, except in the most extraordinary of circumstances.

Many disclosures made by a physician to a patient are distressing; they range from telling a patient he has an incurable disease to revealing the finding of hemorrhoids. None of these has of itself been found actionable by the courts. The important element not found in these cases is so-called foreseeability. A patient may suffer harm after disclosure that he harbors the 47,XYY trait, for example, by committing suicide. It is inconceivable that the physician will be held liable for such harm due to this disclosure unless this result was foreseeable by the physician. In the *Nishi* case the evidence of the standard of good medical practice revealed that severe aggravation of a pre-existing condition would be a foreseeable consequence of disclosure. Nevertheless, this must be seen as an extraordinary situation.

On the other hand, assume that the physician takes it upon himself to omit findings he has made, presumably for the reason that they may be traumatic. On a purely practical level, once the patient does discover these facts, it is possible his trust in his physician will be irreparably shattered unless the physician convinces him nondisclosure was for the patient's own good. In the legal context, it may be true that in the absence of a battery action based on the lack of a fully informed consent the patient may not have an action due to lack of damages, but it is not difficult to picture a patient who is seeking injunctive relief parrying for full disclosure by his physicians. Patients have the legal right to review their medical records when kept in hospitals.[26] Extending this to all findings of a physician is not inconceivable. In the future amniocentesis may be restricted solely to the hospital setting. The right of patients to know all the results of such tests should be further reinforced by the American Hospital Association's Patient's Bill of Rights of which the patient's right to know is a firm precept.[27]

Physicians may argue that a little learning is indeed a dangerous thing. They may say that disclosing such findings as sexual aberrations or the gender of a fetus as found upon amniocentesis should add nothing to the information needed by a patient to make a decision, in this case to seek an abortion. If anything, the medical profession could argue, such disclosures lead to nothing but unwarranted controversy and confusion. On balance, the right of the patient to know about findings pertinent to him must outweigh a physician's perceived notions as to the effect of his disclosure, except, of course, as noted above, in that instance where severe physical distress will follow the disclosure and is foreseeable. It must be underscored that to be actionable the infliction of foreseeable distress must be upon the patient. It would be extremely unlikely that this would allow parents to sue following alleged revelations regarding their child.

Inclusion of genetic data in the medical record

A more delicate subject involves the inclusion of genetic information in the medical record. Despite the confidential nature of the record to those outside the health care–delivery system, this is often not the case for professional eyes within the system. Opinions of geneticists are mixed. One extreme is the statement that the scientific value of having accurate records and being able to exchange data thereon with other researchers far exceeds the consideration of protecting the rights of the individual patient. Other commentators would again segregate sexually and psychiatrically based data into records inaccessible to all but the attending physicians either on sheets to be removed in the record room or in private computer banks. This would prevent accidental release of information to insurance companies or other agencies which could cause the patient to be under a social debility. One physician would require removal of such data should the record be subpoenaed. The legal basis for this latter recommendation appears extremely murky since once in the record, and with the assumption the patient has consented to the release of information in his record, no privilege is available to the hospital for retaining such information in secrecy. If the law allows the patient to see his own record, it must follow that the record must be shown to anyone the patient designates.

Most physicians feel that genetic data should be treated precisely like the traditional family or personal history is treated. Information included should primarily be related to the provision of an adequate diagnosis with other information only being included at the discretion of the physician. This latter view again appears to comport with traditional duties and responsibilities of a physician to his patient. To this opinion one physician added a suggestion applicable to all medical records. He stated that with the increasing mobility of patients today and the lack of continuity of the doctor-patient relationship, the medical record should be given to the patient with an additional requirement that the physician provide a statement regarding observed genetic defects which may be genetically transmissible. A physician doing so will incur no legal liability, as noted above, except, of course, in that rare case when disclosure will lead to foreseeable harm to the patient.

Disclosure of genetic data to third parties

The physician has an ethical duty, as noted previously, not to disclose information he has gathered

about his patient. This duty is probably not breached if a particular patient's genetic data is published in a research journal as long as the patient's identity remains anonymous and the data are related to the study.

Other disclosures to third parties without the patient's consent may be legally actionable if the patient has been harmed. Defamation is defined as a written or oral communication to a third party tending to injure the reputation of the person defamed. Truth is an absolute defense in a defamation action. However, assume for the moment that the finding disclosed to the third party about the patient was erroneous. For example, a patient could predicate a suit in defamation against a physician or genetic counselor who discloses the erroneous fact the patient has an 47,XYY constitution to the patient's relatives, friends, or governmental or social service agencies without the patient's consent, in the hope that these parties will attempt to aid the patient. The patient may argue that his reputation as a peace-loving citizen has been damaged. The physician or counselor may respond that he has a qualified privilege for his actions, thus barring a defamation action since his disclosure was justified to establish a euthenic environment for the patient. Justification as a defense of defamation usually involves disclosures necessary to protect the community such as disclosure of a patient's contagious disease. The case of *Simonsen vs Swenson*, 177 NW 831 (Nebraska, 1920), presents a good example of this. In this case the physician disclosed to this patient's landlady the finding of contagious venereal disease. The landlady subsequently evicted the patient. The court found that the communication fell under the qualified privilege of disclosure to third parties. However, the court did state that, in the absence of such a privilege, the physician could have been found civilly liable for his action since betrayal of a professional secret to the detriment of a patient was a ground for revocation of a physician's license and a breach of trust. Whether something so speculative as the threat of an aroused 47,XYY individual to the community is sufficient justification for the disclosure of such data may be debated.

Where unauthorized disclosure has been made, the patient may also base a suit upon damages caused by invasion of his privacy. A physician or counselor who commercially exploits a patient's genetic defect(s) will probably be held liable for causing the patient humiliation and unwarranted public exposure. The key to an invasion of privacy action is unjustified placement of the patient in the public spotlight. Disclosure to family members probably will not satisfy this requirement. Disclosure to governmental or social service agencies such as community mental health organizations may come closer to satisfying this requirement to predicate an action or invasion of privacy.

All physicians at the symposium agreed with the general statement of the law that beyond disclosure to patients, recording upon the chart, or publication in research journals where patient anonymity has been assured, privacy precludes revealing genetic information to any other sources without the patient's consent, unless there exists specific legislation based upon sufficient data to show that the need for dissemination of the information outweighs personal rights of privacy. This should apply even to public health screening programs that release information to other governmental agencies.

As a final comment regarding disclosure to third parties, professional or otherwise, one professor would divulge information only if the recipient is trained to influence the behavior of the individual concerned, the family, or the physician. The recipient, he stated, must have a thorough knowledge of the total impact of the genetic situation in terms of emotional, social, and financial aspects. He stated that the family physician himself often does not possess this competence.[18] Perhaps this geneticist would only disclose information to experienced genetic counselors. While this may be a good suggestion from a sociologic and scientific viewpoint, this would appear to breach the right of privacy of the patient as well as the patient's right-to-know data pertinent to him in an uncensored manner.

Courses of action available after disclosure of genetic data to the individual

Abortion after amniocentesis. Today, if full disclosure of the findings of amniocentesis to the patient-mother is assumed, the current state of medical progress allows individuals only two alternatives should genetic defects be discovered: do nothing and produce and care for a child who may or may not be defective or seek an abortion. In two cases: *Roe vs Wade*, 93 S CT 705, 1973, and *Doe vs Bolton*, 93 S CT 739, 1973, the United States Supreme Court laid down guidelines concerning the extent to which states can regulate abortion. In the first trimester of pregnancy the state may not regulate or prohibit abortion. This decision is based upon the patient's right of privacy. The United States Supreme Court found this to be a fundamental concept of personal liberty as guaranteed by the due process clause of the fourteenth amendment. In the second trimester the state may enact statutes intended to protect the health of the mother. In the third trimester a state can regulate abortion, or even prohibit it, except where abortion is necessary to preserve the life or health of the mother.

Within this legal framework it would be wise to explore the specific medical situation. At least one case has held that there is no established standard of care when advising the mother of a potentially defective fetus to undergo an abortion.[29] The usual advice given if the amniocentesis reveals a significant genetic defect is that the woman should procure an abortion. Given the time needed for development of the cellular cultures and making the chemical assays and photograph (usually 2 to 4 weeks), the physician is upon the horns of a dilemma. He can advise the amniocentesis early in pregnancy, risking greater chance of infection, etc., but leaving greater time for the analysis or reaspiration in case of failure. On the other hand, he can wait until the fifteenth week, lowering the risk of untoward results from the procedure itself, yet perhaps allowing insufficient time to obtain an abortion if the results are delayed but positive.

Fuchs, co-developer of the technique, has stated that amniocentesis should never be carried out unless the parents are willing to act upon the results. If the parents are willing seriously to consider abortion upon disclosure of positive results such facilities must be readily available. The recent Supreme Court cases cited above forbid state regulation of the use of abortion but conscience clause legislation may militate against this. In one of its opinions the Court left untouched a section of the Georgia statute which stated that private hospitals and their health personnel could refuse to perform an abortion if doing so violated their consciences.[29] Thus, abortion on demand has not become a reality and delay in finding readily available facilities, aside from patient inconvenience, has medical implications as well. Medical authorities agree that the abortion after amniocentesis should be done no later than the second trimester, weeks 12 to 24 of the pregnancy. As noted, the Supreme Court cases allow second-trimester abortions but states can still restrict abortions after this time period. This places the amniocentesis and subsequent abortion on a rigid time schedule, allowing little margin for error or delay in the results, since the optimum time for the amniocentesis is at 15 weeks.

Another matter is the impact of erroneous results. If the results of the tests are reported as positive for a genetic defect but are, in fact, erroneous, an abortion may be procured and the products of conception may be found negative for genetic defects. Here the physician may be in a delicate position. He can stand upon his statement of prior reservations as to guarantees, if he has noted these in the consent form and made them clear in his discussion prior to amniocentesis. This, of course, will not insulate him from liability if the erroneous results were caused by his own actions which fell below the standard of care for the procedure. The possibility of a wrongful death action may be considered by the parents but is of doubtful success, given that the Supreme Court refused to resolve the issue of whether such a fetus is a constitutionally recognized "person."[30]

At the other extreme is a reported negative result but the baby born is malformed or biochemically defective due to genetic defects which could have been noted by the assays following amniocentesis. Again, the parent's suit in malpractice may be entertained if the doctor or the laboratory has not achieved the standard of care in the field. Militating against this is the requirement that the parents show that because of this breach of the standard of care they have been harmed in a manner the law recognizes.

Suits for wrongful life have been tested judicially. In an area unrelated to this present topic but giving a clue as to judicial thought in this situation, the child born out of wedlock brought a damage claim against his father for emotional distress. The Illinois Appellate Court in *Zepeda vs Zepeda,* 190 NE 2d 849, 1963, denied the claim: "Encouragement would extend to all others born into the world under conditions they might regard as adverse."[31]

Four years later, the New Jersey Supreme Court was faced with a problem dealing directly with wrongful life and alleged medical malpractice. In *Gleitman vs Cosgrove,* 227 A 2d 689, 1967, a mother contracted German measles one month after conception. She told her physicians of this condition and they stated that it would have no effect upon the delivered child. Claims were asserted on behalf of the child and the parents since the child was born with severe speech, sight, and hearing problems. The New Jersey Supreme Court rejected all claims. As to the child, the court found no cause of action since, absent the negligence of the physicians, the child never would have been born.[32] The court's reasoning followed *Zepeda* in disallowing any claim for damages for adversity of birth, assuming no malpractice leading to prenatal injury. As to the parents, the court found the decision against them necessitated more extensive discussion. The parents had argued that the emotional impact of rearing a defective child would have been eliminated had the physicians told them the true extent of the possible fetal disability. Had they known, the parents contended, they would have sought an abortion, which, according to New Jersey law at that time, would not have been a criminal act under the circumstances. The court rejected this claim on the grounds that damages in this case would be difficult to measure.[33]

On a more philosophic level, the court went on to state that it would be against the public policy to compensate for the failure to take a fetal life, despite the fact an abortion would be legal. The court went on to note the various famous personages who suffered from hereditary or congenital handicaps and overcame these to lead productive lives. If given the choice, the court reasoned, an individual would rather live with defects than have no life at all. The right to life thus outweighs any emotional or financial burden upon the parents. At least as to wrongful life judicial opinion would appear to insulate the physician or laboratory from liability for errors in the results of amniocentesis.

Other jurisdictions have also rejected this type of action. In *Stewart vs Long Island College Hospital,* 283 NE 2d 616, 1972, recovery was denied a patient for a hospital committee's failure to advise a patient that the fetus was defective and abortion indicated. The hospital was successful in its argument that the law did not recognize the idea of wrongful life. In *Wilmington Medical Center, Inc. vs Coleman,* 298 A 2d 320 (De Sup Ct, 1972), a pregnancy ensued after the failure of a tubal ligation for sterilization purposes. Again, the court here did not recognize a case predicated on wrongful life since damages would be too speculative of definition.

This, however, is not to say that another court may reach a different opinion. Parents availing themselves of amniocentesis should be granted relief if, by negligence, a defective child is produced. Many articles in the medical literature concern indications of a defective fetus and the magnitude of these defects. A standard of care should be developed for determining when an abortion should be advised and when it should not. Also it should not be enough for courts to list the famous people who suffered from genetic diseases or defects and overcame them. Apparently, many courts are stymied in regard to determining damages since costs of raising a defective child could be offset by the child's future productivity.[34] Many genetic defects produce individuals who can be nothing but a burden to themselves, their families, and society. Their potential usefulness or enjoyment of life is nil.[35] It should not be beyond the scope of a court to determine the financial burden of rearing such an individual since offsets are not involved. Many defective children are placed in state-run institutions. In these cases the financial burden (and damages possible in a court action) is lessened. This may be the mechanism by which parents can be entirely relieved of the economic hardship of caring for such a child.

Voluntary sterilization. Voluntary sterilization, whether or not as a means of genetic control, is not forbidden in any state.[26] Some states do regulate it somewhat in terms of age of the patient or the requirement that a doctor perform the procedure.[36] Other states which had forbidden voluntary sterilization except when a medical necessity have repealed such acts.[37] In *Jessin vs County of Shasta,* 274 Cal App 2d 737, 1969, the court found voluntary sterilization to be constitutionally protected from infringement by the state under the right to privacy. Voluntary sterilization is also no longer considered a form of mayhem in depriving oneself of the ability to fight for his sovereign.[38]

Griswold vs Connecticut, 381 US 479, 1965, has probably prevented the possibility that a state could make it criminal for an individual to advise sterilization as a means of postmarital contraception, based upon the right of privacy.[39] *Eisenstadt vs Baird,* 92 S Ct 1029, 1972, has probably done the same when advising unmarried individuals. In the latter case, the United States Supreme Court upheld the Court of Appeals which had reversed a felony conviction of a person who had dispensed a nonprescription contraceptive foam after a lecture at Boston University on population control. Baird had dispensed such foam to unmarried women in contravention of a Massachusetts statute. The Court found that the right of privacy protects all individuals, married or single, from unwarranted governmental intrusion into matters so fundamentally affecting a person as the decision whether or not to bear or beget children.

Whether there is a right to voluntary sterilization on demand will probably depend upon whether the institution at which it is sought is private or governmental. In *Hathaway vs Worcester Hospital,* 72-1114, First Circuit of Appeals, 1973, the court cited the cases of *Eisenstadt, Roe,* and *Doe* and stated that, "We are merely saying that . . . once the state has undertaken to provide general short-term hospital care, as here, it may not constitutionally draw the line at medically indistinguishable surgical procedures that impinge upon fundamental rights. Accordingly, we reverse (the district court's dismissal of the action) and remand for entry of an order declaring the Worcester City Hospital's policy against the use of its facilities in conjunction with sterilization operations is unconstitutional."[40] Private hospitals though can determine their own policies with regard to sterilization.

The state and involuntary sterilization. Negative eugenics is a conscious attempt to reduce the number of deleterious genes in the gene pool.[41] Involuntary sterilization statutes are examples of legislating negative eugenics. By their application such statutes prevent certain individuals from procreation. The right of procreation is not mentioned in the Constitution but

decisions of the United States Supreme Court have stated that this, nevertheless, is a fundamental right.[42] The due process clause of the fourteenth amendment of the Constitution protects citizens from unwarranted infringement of fundamental rights by states. For a state to abridge a fundamental right it must have a compelling interest.[43] The state is also required to achieve its goal by rational means. The state could argue that its legislation seeks to improve the quality of life by reducing the number of individuals who suffer and are burdensome to others. While this may be a compelling state interest the means used may be attacked as being based on a distinct paucity of scientific evidence.[44] Mental retardation, for instance, due to a genetic defect, is often a recessive condition. To be expressed in the offspring of a retardate means the sexual partner must also carry at least one similar defective gene, often an extremely rare occurrence. If the mental retardation is due to a dominant trait this would appear to strengthen the rationale for sterilization since procreation with any partner would have a high a priori probability of producing a similarly affected offspring. However, mental retardation that is dominant is not only extremely infrequent but also highly likely to be associated with other genetic debilities usually rendering the possessor incapable of reproduction. Thus, except in the case of individuals whose mental defect is caused by a dominant gene and who are capable of reproduction, the preclusion of procreative potential appears an irrational legislative method of obtaining an arguably rational goal of preventing the genetic transmission of defects.

The legislative bases for sterilization laws often include the provision that sterilization is for the ease of caring for a defective individual and the prevention of irresponsible parents whose children often must be cared for by the state.[45] Earlier decisions found involuntary sterilization an exercise of the police power not offending constitutionally guaranteed due process. The Kansas court found its sterilization statute in the public interest.[46] Idaho and Nebraska found this use of the police power applicable as a way of furthering the good of the community as a whole.[47, 48] The Michigan court stated that, "No citizen has any right (to procreate in this case) superior to the common welfare."[49] The United States Supreme Court validated this power in the celebrated case of *Buck vs Bell,* 274 US 200, 1927.

While sterilization statutes remain on the books the judiciary in many states is slowly turning away from frequent utilization of such statutes, often on procedural grounds. In *Frazier vs Levi,* 440 SW 2d 393, 1969, the mother of a retarded girl petitioned the court for her daughter's sterilization. The Texas court denied her request, stating that an incompetent ward does not have legal capacity to make such a petition and her guardian does not have legal authority. This decision thus restricted petitions for sterilization to state agencies. Some states, however, would allow a natural guardian to consent just as for other medical procedures.[50] A question to be raised here is whether a physician would perform the procedure, even with the consent of the guardian, without further assurances that the consent will not be found invalid at a future date and possibly render the physician liable for an "unconsented to touching."

Not all courts are retreating from involuntary sterilization legislation. The case of *In Re Cavitt,* 157 NW 2d 171, 1968, from Nebraska, should be noted. Here, the mother of eight children was confined to an institution for the mentally deficient. Sterilization was made a prerequisite for her release.[51] According to the Nebraska statute a Board of Examiners of Mentally Deficient made up of five physicians from state hospitals is delegated the power to decide if sterilization is necessary for release from an institution, based on its psychiatric evaluation of the patient (to determine if the patient is mentally defective) and its physical examination of the patient (to determine if the patient is capable of procreation). After the procedure is performed, witnessed by a member of the Board, certification of the sterilization is placed in the public records of the State Department of Health. The Nebraska Supreme Court upheld the statute in a curious three-to-four decision. (The Nebraska procedures acts require that for the state supreme court to rule a statute invalid there must be the concurrence of five of the seven justices.[52]) The three justices did not find an unlawful delegation of power to the Board. Their opinion further stated that mandatory sterilization in this case was a valid exercise of the police power. While acknowledging that procreation is a fundamental right, the three found its infringement was based upon a compelling state interest in furthering the good of the community. Finally, in a statement that militated against the presumption that the statute was, in part, based upon genetic considerations, the court held that it would not be necessary for the state to demonstrate that children born to this woman would inherit her mental subnormality.

Due process guarantees must be complied with in sterilization cases and are included in most sterilization statutes. These consist of the following: (1) A hearing must be held; (2) adequate notice of the hearing must be given the candidate; (3) a guardian must be appointed if the candidate does not have one.[53] Since individuals subject to involuntary sterilization are often indigent and of necessity incompetent, by analogy to

juvenile law, right to counsel may also be required.

The United States Supreme Court has not reviewed this area since *Buck vs Bell.* Since the time of that opinion the scientific basis of involuntary sterilization as a method of eliminating deleterious traits has been weakened.[54] The Court's subsequent and repeated pronouncements on procreation as a fundamental right may make a state's proof that it has a compelling interest for infringing upon this right and a rational method to do so a most difficult task.

In *Holmes vs Powers,* 439 SW 2d 579, 1969, the Kentucky court held that where the state has no sterilization statute and the would-be patient is incompetent she herself cannot legally consent to the procedure. In the absence of statute, a court order is not enough to insulate the parties from liability for an involuntary sterilization. A graphic example of this is the case of *Wade vs Bethesda Hospital,* 337 F Supp 671 (DC3D Ohio, 1971). Here, the court found a state probate court judge personally liable in damages for ordering the compulsory sterilization of an incompetent minor. The judge pleaded in defense that he must be granted immunity from suit since he, at most, exceeded his jurisdiction. The court found that in the absence of enabling legislation the judge had no jurisdiction at all over this matter and, therefore, was not immune. As dicta the court added that, although Ohio had no statutes forbidding sterilization, bills proposing compulsory sterilization for incompetents had arisen at numerous times since 1925 in the legislature and had been consistently defeated. Therefore, the judge had no legal authority to act upon the petition of the local county welfare board.[55]

The final determination of this case did not include the hospital or the physicians who performed the surgery. It is possible that these parties settled out of court. The complaint of the plaintiff did suggest a possible ground for liability on the part of the hospital and the physicians. The complaint charged a conspiracy by all parties to deny the plaintiff her civil rights (as codified in 42 USC, 1983) under cover of state law by seeking the aid of the state probate court judge in furtherance of their scheme.

This last issue of the potential liability of health personnel in the field of genetics raises a good point. In the minds of most physicians doing what is best for the patient is of primary importance. Motivated by this goal, disclosures may be made to inappropriate persons or, as in the *Wade* case, sterilization may be sought. It is highly probable that in an effort to aid the patient physicians may not realize they are performing acts to which legal sanctions attach. No aspersions should be cast upon medical altruism. It is, however, imperative that physicians become aware that they operate in a legal as well as a medical framework and that medical goals must be seen in the light of the legal safeguards of personal liberty.

Prohibitions on marriage. States have also enacted statutes prohibiting the marriage of certain individuals, again presumably partially based on genetic considerations. For instance, Washington and North Dakota prohibit the marriage by a woman under 45 or a man at any age, unless he marries a woman over 45, if either one is imbecilic, insane, a habitual criminal, a common drunkard, or feebleminded or has hereditary insanity.[56] As with most negative eugenics legislation, the scientific basis for the statutes is weak. Criminality and drunkenness have not been shown to be inheritable. Even scientists who believe the 47,XYY syndrome can cause aggression and consequent criminal behavior are aware of the limited possibility that 47,XYY can be genetically transmitted and expressed in an affected individual's offspring. Perhaps the inclusion of these traits is a reflection of the legislature's notion that these people would become poor parents. But the statutes are silent as to when statutes such as noted above are gained or lost. Due process guarantees in the Constitution demand that statutes be written with sufficient clarity and exactness as to be capable of specific application. It would appear that these acts are vulnerable to constitutional attack for vagueness and overbreadth. Besides this, nothing in the statutes prevents procreation by the named classes of individuals without the benefit of marriage.[57]

All states ban marriages between members of a direct lineal line and 30 states extend this to prohibit marriages of first cousins.[58] Presumably these statutes are grounded upon medical evidence that the offspring of such unions tend to be genetically inferior. While such evidence has been questioned there is no trend toward easing such restrictions. Furthermore, these restrictions are often reinforced by incest statutes which carry severe penalties. Genetically it is true that by virtue of common ancestry recessive genes of both partners will have a greater statistical probability of expressing themselves. By the same token if the ancestry is sound the child of such a union receives a double genetic benefit. Thus, it is not the consanguinity of the parents which causes a defective offspring but the presence of a deleterious recessive gene in the ancestry. The question must be asked again whether a state can show a compelling interest for infringing upon the right of lineal descendants or first cousins to marry and procreate and, if it does, whether its method of achieving this goal is rational. Like involuntary sterilization legislation, prohibitions on consanguinous marriages based

purely on genetics rest on weak scientific evidence where the genealogic records of the prospective mates are free of deleterious influences.

Another legislative attempt to prohibit marriage is the antimiscegenation statute. This type of legislation is based upon the fallacious assumption that positive genetic characteristics of any race cannot be achieved if the races are mixed. The United States Supreme Court in *Loving vs Virginia,* 388 US 1, 1967, held such legislation unconstitutional because such a legislatively created racial classification was without a compelling state interest. At least one commentator feels that banning such negative eugenic statutes as this advances the state's goal of eliminating deleterious traits, if not deleterious genes, by providing for the introduction of new, advantageous genetic combinations into the gene pool.

Conclusion

More and more genetic information is being obtained about specific individuals through amniocentesis, interviewing, and screening. Despite the fact that physicians currently feel certain findings must be kept confidential, for the most part patients will become aware of their individual genetic complements. The receipt of such knowledge imposes duties and responsibilities upon the recipient to act upon such knowledge. Data collection qua data collection would appear a futile exercise of scientific curiosity. The final question of this paper then must be whether a price must be exacted for the genetic information an individual receives, solicited (amniocentesis or interviewing) or not (screening).

At present, it appears that as long as there is a fundamental right to procreate the possibility that a state-sponsored eugenic program will become a reality is very small. Negative eugenics programs in existence today, as noted above, are not effective as a method of eliminating deleterious traits in future generations because of their poor scientific bases.

Positive eugenics programs would go beyond the goals of negative eugenics and seek to ensure that superior genes would be propagated. A program such as this would involve the encouragement of people with so-called superior genes to procreate via marriage and the discouragement of the marriage between individuals with "inferior genes." While such a goal may arguably be within the purview of the state to maintain and improve the health and welfare of its citizens, any compulsion to such a goal would be vulnerable to constitutional attack. Due process guarantees in the Constitution prohibit the infringement of fundamental rights without a compelling state interest. A positive eugenics program would have to prohibit the procreation of certain people deemed inferior. Positive eugenics sits upon scientific bases even more speculative than those of negative eugenics. It is doubtful a compelling state interest could be predicated on such a notion.

A positive eugenics program would also involve classifying individuals according to their genetic make-ups. Chief Justice Burger has said that in applying the equal protection clause of the fourteenth amendment to exercises of the state police power, the Supreme Court will check to see that the criteria for placing people in different classes are reasonable and not arbitrary, with the goal of the legislation kept in mind.[59] Determination of traits in order to classify individuals would appear at present fraught with unreasonableness and capriciousness. Since man is a complex physical and intellectual entity, a selection process not offensive to constitutional guarantees appears an insurmountable dilemma. Even if traits to be selected are scientifically neutral subjectivity will enter the picture through the social judgments of the selectors. The late Professor Herman Muller, a Nobel laureate in genetics, member of the Columbia University genetics group, and advocate of positive eugenics legislation, provides a good example of this. His lists of attributes he felt should be propagated were creative intelligence, a cooperative disposition, and robust health. Yet the famous personages he felt met these standards kept changing with the professor's political alterations from Lenin and Marx in his early career to Lincoln and Descartes as he grew older.

The uses of genetics must be viewed in the light of constitutional guarantees afforded all citizens. Fundamental rights as currently enumerated by the United States Supreme Court must be protected from unwarranted infringement by states. People must not be classified by means of arbitrary and scientifically speculative criteria. Other rights not found specifically in the Constitution must be respected as well. While patients must have a right to know data pertinent to them their privacy must be protected from unwarranted invasion.

With such a legal framework as currently exists the best approach in dealing with genetic information and the best method of bringing about the utilization of such data would appear to be the exertion of peer pressure after the citizenry is educated as to the burdens of rearing a defective child and the means to prevent it. This does not necessarily mean that society should encourage all carriers of deleterious genes to seek voluntary sterilization. Few people exist who are not carriers of some defective traits, usually in a masked recessive state. This does mean, however, encouragement of

judicious application of screening, counseling, and amniocentesis.

Cystic fibrosis can serve as a good example of this. Premarital screening can detect those individuals who carry the recessive gene for cystic fibrosis. These people could be advised of the defect in hopes their choice of mate will reflect this information. If the chosen mate was recessive for the cystic fibrosis trait, then amniocentesis could be helpful after conception to determine if the fetus was definitely affected. By combining these two procedures, the carrier couple, assumedly more enamored of each other than of cytogenetics, could still plan for a normal family with abortion eliminating the risk of producing children with cystic fibrosis. The final choice, of course, must be left to the individuals themselves. But if wise choices are not made the genetic price to be exacted later may be astronomic.

In closing, euthenics, the science of making the environment or living conditions better, especially for those with defects, must be discussed. An obvious example of euthenics is providing eyeglasses to people with poor vision. Euthenics is a function of a more and more sophisticated and compassionate society which sees help to the disabled as a public policy. While only the most callous would take issue with the progress of our society in this matter, euthenics often runs counter to another notion, stability and evolution of the gene pool. It may be difficult to enact eugenics legislation despite the fact that, however misguided, it is aimed at eliminating deleterious traits while enabling beneficial traits to abound. Euthenic legislation is much easier to enact, but its effects can be negative. In the short run, euthenics is often very expensive.[60] In the long run, euthenics can potentially lead to genetic deterioration.

Natural evolution tends to remove defective genes from the gene pool by removing individuals with these genes before the reproductive ages, through death. Public sentiment which encourages the granting of aid to medical research has the ultimate effect of keeping such individuals alive and comfortable well into the reproductive years, allowing them to transmit their deleterious genes. The diabetic patient, the hemophiliac patient, and many types of people with genetic biochemical imbalances today all have the opportunity for a normal existence. The prolongation of the lives of these people is an asset to society in the potential productivity of these individuals. However, repeated transmittal of their defective chromosomal complements may so increase the genetic load in man (the deleterious genes that he carries) as to irreparably weaken the species. Currently, the thought of curtailing euthenic activities would appear barbaric. It must be hoped that soon the popular appeal of euthenics can be at least partially channeled into eugenics before man's science and compassion are the cause of man's undoing.

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This section is suitable for reporting results of therapeutic trials, descriptions of new procedures or instruments, and case reports which illustrate a principle. Reports should be limited to seven hundred words and two references. Use of an illustration or table requires a proportionate reduction in total words.

Ultrasonic detection of combined pregnancies

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COMBINED INTRAUTERINE and ectopic pregnancies have always been felt to be a rare occurrence, with an estimated incidence of 1 in 30,000 pregnancies.[1] However, reports in the literature of combined pregnancies have increased and a survey by this author notes 549 such cases reported to date. A suspicion that this entity is under-reported and probably underdiagnosed is supported by the extreme difficulty in making the diagnosis of a combined pregnancy on clinical grounds. The patient usually presents with symptoms which turn one's attention to the presence of an ectopic pregnancy; however, the absence of vaginal bleeding can be a clue to the presence of an intrauterine pregnancy during the first trimester. Clinical criteria for making the diagnosis were reviewed by Winer, Bergman, and Fields[2]; in their series the correct diagnosis on clinical grounds was made in only 9.9% of the cases. Most often, suspicion of the presence of an intrauterine pregnancy first appeared only at the time of laparotomy. Two cases of combined pregnancy are presented here, occurring within 6 months of each other; both were diagnosed only at the time of laparotomy. However, the intrauterine pregnancy was confirmed by ultrasonic investigation of the intrauterine cavity and persistently elevated serum human chorionic gonadotropin (HCG) levels after salpingectomy.

A 28-year-old white woman, gravida 9, para 2, with a history of six miscarriages, presented with an acute onset of severe, constant, sharp abdominal pain in the left lower quadrant without vaginal bleeding. The last menstrual period (LMP) was 45 days prior to admission. In the preceding 2 weeks the patient felt pregnant, with breast engorgement, nausea, vomiting, and weakness. She had no prior history of pelvic infections and had a strong family history of multiple births.

Physical examination was remarkable only for left lower quadrant abdominal tenderness without rebound. No masses were palpable nor could the uterine fundus be felt. The cervix was soft and pain was elicited on motion. No bleeding was noted. Her serum HCG was 50.5 IU. While she was in the hospital her hematocrit dropped from 37.0 to 35.4, accompanying a recurrence of abdominal pain, with passage of 50 cc of clotted blood per vaginam. Laparoscopy revealed a hemoperitoneum of 200 cc, and on laparotomy a left ampullary tubal pregnancy was present without obvious site of rupture. A left salpingectomy was performed. The uterus was enlarged to 8 weeks' gestation size and a solitary corpus luteum was noted on the left ovary. Pathologic studies confirmed the presence of a tubal pregnancy. One week postoperatively the serum HCG was 80.6 IU and ultrasonic examination verified the presence of an intrauterine pregnancy with a gestational sac consistent with 8 weeks' size. On discharge the intrauterine pregnancy was continuing uneventfully.

An 18-year-old nulliparous white woman presented with an episode of acute left lower quadrant abdominal pain without vaginal bleeding. The LMP was 55 days prior to admission. She denied a history of pelvic inflammatory disease. Physical examination revealed severe left lower quadrant tenderness with rebound tenderness. Again masses or uterine size were difficult to delineate. On admission her hematocrit dropped from 36.0 to 27.8. Exploratory laparotomy revealed 2,000 cc of clotted blood. A left salpingectomy was performed for a ruptured ampullary tubal pregnancy. Once again the uterus was found to be suspiciously large at time of laparotomy, and postoperative ultrasonic examination revealed an intrauterine gestational sac consistent with 8 week's size. In both instances the ovaries were spared to protect the corpus luteum of pregnancy. In the second case the patient later elected an abortion of the intrauterine pregnancy.

The diagnosis of combined pregnancy will not be made unless the entity is considered for all patients suspected of having an ectopic pregnancy, especially in those with the atypical presentation of having no vagi-

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nal bleeding, and where the uterine size is larger than expected for an ectopic. In both cases presented, the diagnosis could have been made by preoperative ultrasonic examination. With the increased availability of diagnostic ultrasound, I suggest that all such patients receive such scans as part of their routine workup, in addition to postoperative monitoring of serum HCG levels, which is useful in those early cases where the results of the intrauterine scan can be inconclusive.

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Leiomyoma of the fallopian tube: A cause of tubal pregnancy

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LEIOMYOMA of the oviduct causing ectopic tubal pregnancy is a rare condition in clinical practice. An example of this exceedingly rare occurrence is herein reported.

A 33-year-old woman came to the emergency room because of a lower abdominal pain associated with vaginal bleeding and syncope. She was para 1-0-0-1, her menses were always regular, and the last menstrual period occurred 48 days previously. The pain had lasted for 7 days and was accompanied by spotty vaginal bleeding for the last 4 days. The pain became severe and the bleeding heavy on the day of admission. Six hours before the patient's arrival in the emergency room, some "tissue or liverlike clots" were reportedly passed through the vagina. On physical examination, she was found well developed, in moderate distress, but alert and oriented in time, place, and person. The pulse was 100 bpm and regular and the blood pressure was 130/60 mm Hg, both in the recumbent position; in the sitting position these values changed to 140 and 90/50, respectively. The temperature was 37° C and respirations were 40 per minute. The oral mucosa and conjunctiva were pale. The abdomen was slightly distended and tender. Rebound tenderness and shifting dullness were demonstrated; the audible bowel sounds were decreased. The vagina contained dark blood. Tbe cervix was closed; it was cyanotic and tender to lateral motion. The cul-de-sac and left adnexa were bulging and tender to palpation. The uterine contour and adnexal masses could not be appreciated because of marked tenderness. The hemoglobin was 10 gm/100 ml; the hematocrit was 30 vol. %. A urine pregnancy test was positive.

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Fig. 1. Leiomyoma of the proximal portion of the fallopian tube (left). Adjacent and just distal to it, a hemorrhagic area of the ruptured pregnancy is seen. Note also a separate small serosal myoma at the inferior aspect of the tube, and normal middle and distal thirds of the organ. A small hydatid cyst of Morgagni is seen close to the infundibulum.

Emergency laparotomy was performed, with the clinical diagnosis of left ruptured ectopic pregnancy. The abdominal cavity contained about 1,000 ml of mostly clotted blood. The left tube revealed a 3 by 3 cm round firm mass situated 2 cm distal from the uterine cornu. Adjacent and just distal to the mass, a ragged hemorrhagic soft area, 1 cm in size, was noted. The middle and distal thirds of the tube appeared normal. The left ovary showed a 5 cm cyst. The uterus was soft and slightly enlarged; it did not show myomas. The right ovary was represented by a palpable streak of tissue only, and the right tube appeared hypoplastic. Left salpingectomy and left ovarian cystectomy were performed.

Seen in the pathology laboratory, the fallopian tube measured 9 cm in length and 1 cm in width. The proximal part of the tube showed a 3 by 3 by 2.5 cm leiomyoma (Fig. 1); the tumor was seen partially embedded within and partially projecting outside the wall of the tube. Another small serosal myoma was attached to the tube by a slender fibrous pedicle. Just distally to the larger myoma, the wall of the tube showed the implantation site with decidua and chorionic villi. Rupture and extensive hemorrhage were evident in this area. The entire remaining fallopian tube showed normal gross and microscopic appearance, without any indication of chronic inflammatory process. The specimen of ovary proved to be a corpus luteum cyst.

Chronic salpingitis is the most frequently demonstrated cause of tubal pregnancy. Other rarer mechanical causes have been mentioned in the literature, such as tubal diverticula, extrinsic tumors, intratubal growths, and endometriosis. Leiomyomas arising in the fallopian tube are very rare; most of them are asymptomatic and without clinical significance, although rarely a torsion of a pedunculated tubal leiomyoma may occur with resulting acute abdominal symptoms. Niles and Clark,[1] in their review of 436 ectopic pregnancies, found evidence of an obstructive mechanical

phenomenon other than chronic inflammatory disease in fewer than 1% of the cases, and not a single instance of a tumor of the fallopian tube. Clearly, an ectopic pregnancy attributable to a mechanical obstruction due to a primary neoplasm of the oviduct is a rarity. Three such cases were reported in the older literature.[2] The clinical history and pathologic findings of the patient described by Sehmisch[2] were similar to those of our patient. Sehmisch's patient was a 27-year-old woman, with a history of four uncomplicated pregnancies and deliveries, operated upon because of a ruptured tubal pregnancy associated with a severe hemorrhage, caused by an obstructing leiomyoma of the tube. There was no chronic salpingitis.

The entire tube in our case was examined thoroughly, and it revealed no histologic indication of chronic inflammation, active or healed.

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Asymptomatic cervicovaginal shedding of herpes simplex virus

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HERPES SIMPLEX VIRUS (HSV) genital infections may be asymptomatic during pregnancy and during the early postpartum period.[1] In addition, virus may be recovered from vaginal secretions of nonparturient women in the absence of lesions.[2] The recovery of 2.5 $\log_{10}$ $TCID_{50}$ HSV/ml from cervicovaginal secretions of two women 4.5 and 7 months after primary infection is reported.

Ten women seeking medical attention at the University of Iowa Student Health Center for vulvovaginitis of 3 to 10 days' duration agreed to participitate in the study. None had a history of previous venereal infection. All had a nonreactive Venereal Disease Research Laboratories (VDRL) test for syphilis. Written informed consent was obtained and the study protocol was approved by the Human Experimentation Committee of the Medical College.

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The course of two of these women is reported here. The other eight women, with initial culture-proved HSV infection, were followed in an identical manner for 2 to 6 months but did not demonstrate subsequent cervicovaginal shedding of HSV.

Viral cultures were obtained on the first day of the clinic visit after a thorough pelvic examination by a gynecologist. Subsequent cervicovaginal cultures did not require a pelvic examination. Quantitative cervicovaginal cultures for HSV were obtained by use of vaginal tampons (Kotex, Comfortube, Kimberly-Clark Corp.). Each woman inserted a vaginal tampon for 5 minutes. Virus was extracted and quantitated by means of previously described methods.[3] Subsequent cultures were obtained every 10 ± 4 days when virus had been recovered on the previous culture or every 30 ± 7 days when no virus was isolated from the preceding cultures.

All virus isolates were identified as HSV type 2 by neutralization with type-specific rabbit immune sera.[4]

Over a period of 7 months, 13 cervicovaginal cultures were obtained from a 25-year-old divorced woman with no previous history of genital HSV infection. On day 6 of symptoms, consisting of burning on urination, perineal itch, and vaginal discharge, 6.0 $\log_{10}$ $TCID_{50}$ HSV/ml (Fig. 1) was recovered from the cervicovaginal secretions. The quantity of virus in the cervical secretions gradually decreased to 2.0 $\log_{10}$ $TCID_{50}$ HSV/ml by day 26. Genital symptoms except for leukorrhea had dissipated by day 13 of illness. HSV was not recovered between days 30 and 109; however, after 7 asymptomatic months, 2.5 $\log_{10}$ $TCID_{50}$ HSV/ml was recovered from the cervicovaginal secretions. A pelvic examination at this time demonstrated no vulvovaginal or cervical lesion. Transfer of the patient to another area made subsequent cultures impossible, although she reported by telephone no genital symptoms during the subsequent three weeks.

The second patient, a 28-year-old single graduate student with no previous history of HSV infection, was seen on day 4 of symptoms consisting of inguinal adenopathy, vaginal pruritus, bloody and mucous vaginal discharge, genital pain, and pain on urination. HSV, 5.5 $\log_{10}$ $TCID_{50}$ ml, was recovered from the cervicovaginal secretions. Three days later 9.5 $\log_{10}$ $TCID_{50}$ HSV/ml was recovered. Additional cultures were not possible because of discomfort until day 20, at which time 5.5 $\log_{10}$ $TCID_{50}$ HSV/ml was recovered. Symptoms persisted until day 34. No HSV was recovered from tampon cultures on days 109 and 119.

While the patient was asymptomatic, 2.5 $\log_{10}$ $TCID_{50}$ HSV/ml was recovered from the cervicovaginal secretions at 4 months. After being informed of the culture results she refused additional cultures, but she reported by telephone no genital symptoms in the subsequent weeks (Fig. 1).

Asymptomatic genital shedding of HSV has been documented in both females[1, 2] and males.[5] However, the quantity of virus shed in individual patients has not been recorded. We report the cases of two women who had shedding of 2.5 $\log_{10}$ $TCID_{50}$ HSV/ml when no evidence of infection was apparent.

In the first patient, viral shedding continued after

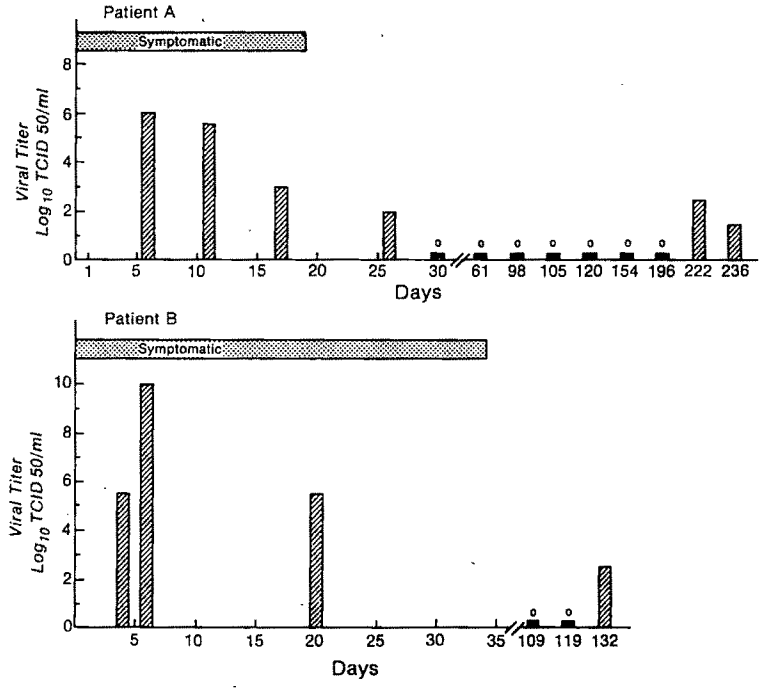


Fig. 1. Duration of symptoms and viral quantitation in two patients with genital herpes simplex virus.

genital symptoms abated. Asymptomatic cervicovaginal shedding of HSV occurred at 4.5 and 7 months after initial infections. When asymptomatic viral shedding occurred, both patients denied exposure to multiple sexual partners or to partners with genital herpetic lesions.

The titer of virus recovered during asymptomatic shedding in both patients was similar (2 $\log_{10}$ $TCID_{50}$ HSV/ml) and was less than that shed during primary infections. The mechanism of viral shedding is not clear. As all isolates were HSV 2, their courses are compatible with reactivation of latent infections or with reinfection. HSV serology was not performed on these women.

These cases demonstrate that asymptomatic genital viral shedding occurs following acute vulvovaginitis. The quantity of virus shed during primary genital infection seems to be much higher than during subsequent asymptomatic viral shedding by the same individual. Additional studies of the patterns of genital viral shedding are necessary to delineate the epidemiology of this common venereal infection, since asymptomatic shedding due to either reactivation or reinfection may be important to the spread of genital HSV.

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Fetal death at term due to lightning

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LIGHTNING INJURY to a gravid woman is a rare event. Several cases, with varied fetomaternal prognoses, have been reported.[1, 2] In only one case was there immediate cessation of fetal movements and subsequent stillbirth 3 to 4 months later.[1] Another similar case is reported and the etiology, prevention, and feasibility of fetal revival in such circumstances are discussed.

The opinions expressed in this article are those of the author and do not necessarily reflect those of the United States Public Health Service or the Indian Health Service.

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Table I. Previously reported cases of lightning injury associated with pregnancy

Year	*Author*	*Age (yr)*	*Parity*	*Gestation (mo)*	*Loss of consciousness*	*Burn marks*	*Effect*
1833	Schieffer	?	? Multip.	8	No. Knocked down	Superficial; over left shoulder, chest, abdomen, legs	Normal delivery at term of living infant
1844	Alexander	?	?	7	No	Small superficial marks on left scapula	Mother and pregnancy remained normal next day. Further progress not reported
1891	Ebertz	28	?	7	Yes	Superficial; right shoulder, arm, breast, abdomen; deeper: thigh	Normal delivery of living infant at term
1906	Torggler	25	2	7	No. Fell off seat screaming	Left scapula, along both sides of back, around abdomen to symphysis pubis and down both legs	Immediate cessation of fetal movements. Macerated stillbirth 3-4 mo later
1959	Samsoenarjo	22	2	6+	Yes	Deep; 8-9 cm in diameter over abdomen, immediately below umbilicus	Rupture of uterus required immediate cesarean section; infant was dead but mother survived
1965	Rees	25	?	2+	Yes. Knocked down	Superficial; entry at back of neck, on right shoulder and over left mastoid region; exit burns; transversely across buttocks	Delivered normally at term
1972	Chan and Sivasamboo	29	G2 P?	Term	Yes	Irregular patch of erythema 8 cm long with wheal on right hypochondrium and paraumbilical areas	Went into labor after accident and delivered 12½ hr later normally; infant was cyanosed at birth and died 15½ hr after birth due to congestive cardiac failure
1972	Chan and Sivasamboo	19	G1 P0	Term	No. Knocked down	Irregular linear areas of erythema with accompanying wheal on lateral aspect on right shoulder, right half of ventral abdominal wall, and on medial aspect of right thigh and over left eyebrow	Went into labor after accident; delivered normally of living infant 14 hr later

A 12-year-old Navajo Indian, gravida 1, para 0, came to Gallup Indian Medical Center at term on August 19, 1977, 2 days after being struck by lightning. While standing outdoors on a cloudy day, she was struck by lightning and was unconscious for 2 to 3 minutes until she was awakened by her relatives. Upon arousal she felt no further fetal movements. Examination revealed fetal death. Spider wave pattern superficial burns were noted over the right palm, extending upward to the right axilla, and then descending along the right lateral chest wall and abdomen up to the right groin, with minimal involvement of the right lower quadrant of the abdomen. She had also a small area of superficial burn on her forehead above the right eyebrow. The burned areas healed spontaneously. Her past and family histories were unremarkable. She had no previous antenatal care. All routine antenatal investigations performed were within normal limits. Seven days later she went into labor spontaneously and was delivered of a macerated male fetus weighing 2,400 grams. The fetus and placenta grossly appeared normal. No autopsy study was performed.

Table I shows the reported cases of lightning injury in pregnant women. The first five cases were reported by Rees.[1] Labor may be induced by the shock or the passage of high-voltage current through the uterus. In advanced pregnancy, lightning can also cause severe uterine contractions, resulting in rupture of the uterus.[1] However, no maternal death was noted in the literature. Both uterus and amniotic fluid are thought to be good conductors of the electric current, which thus reaches the fetus, inducing cardiac arrest.[2]

In adults, cardiac arrest is not infrequent following lightning injury. Indefinite continuance of artificial resuscitation is advised, as frequently complete recovery is noted to occur after prolonged resuscitation. This is true because following lightning stroke the cessation of metabolism in all cells, including brain cells, is so instantaneous that onset of the degenerative process is delayed. Cardiopulmonary arrest, with fixed and di-

lated pupils, frequently noted after lightning injury, and unlike other causes, should not be taken as an indication of cerebral death. Can a fetus in utero be affected in such manner as well (after the mother had been struck by lightning)? Is it possible to resuscitate such a fetus in utero? Perhaps cardiac arrest can be produced experimentally in a fetus in utero by electric shock, followed by an attempt to resuscitate that fetus. If successful, this resuscitation procedure could be made applicable to the human fetus in utero. This could be an exciting field to study and much knowledge might be added to perinatology.

The following preventive measures are recommended when lightning threatens: if outdoors, remove all metal pieces from the head; lie flat or crouch down; move to a safer place—if possible, to a building in the immediate vicinity or to a grove of trees but never a lone tree (lightning bolts frequently strike tall lone trees). Do not remain in water if swimming or boating. If in a car, other than a convertible, stay inside. In a building, the safest place is in the basement; stay away from open doors, windows, telephone, radiators, fireplace, TV, radio, lamps, and other electric equipment; avoid washing dishes or taking showers or baths.

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Spurious elevation of amniotic fluid bilirubin in acute hydramnios with fetal intestinal obstruction

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LILEY[1] HAS cautioned obstetricians of a variety of potential errors in the assessment of amniotic fluid for hemolytic disease of the newborn infant. A case is presented of an elevated amniotic fluid bilirubin level, without evidence of hemolytic disease, in a woman with acute hydramnios. The infant was found to have had an in utero intestinal obstruction.

A 35-year-old woman, gravida 2, para 0, abortus 1, A-Rh negative, VDRL negative, was noted at 34 weeks' gestation to have gained only 5 kg over her prepregnancy weight; her uterine fundus was that of a 26 week gestation. An antibody screen was negative. An ultrasound at that time demonstrated a biparietal diameter compatible with a 35 week gestation fetus.

During the following week she noted increasing abdominal girth and abdominal tenderness. On examination she was noted to have gained 6 kg. Her blood pressure was unchanged and there was no proteinuria. Sonography revealed hydramnios. X-ray of the abdomen revealed no evidence of fetal skeletal anomalies. Liver, renal, and clotting function studies were normal. A 2 hour postprandial blood sugar was normal. A repeat screen for atypical antibodies was negative and a Betke-Kleihauer stain revealed no evidence of fetal-maternal transfusion.

An amniocentesis revealed yellow amniotic fluid, shake-test positive, delta O.D. 0.404 (high upper zone). Alpha fetoprotein and viral cultures were negative. A primary cesarean section was performed under general anesthesia with an estimated 3,500 cc of yellow fluid noted. The placenta weighed 750 mg without evidence of pathologic change.

A female infant, weighing 2,900 grams, at 35 to 36 weeks' gestation by examination, with Apgar scores of 1 and 4 at 1 and 5 minutes, respectively, was born. The infant was pale, with massive ascites and minimal peripheral edema. She required mechanical ventilation. The CBC revealed a hemoglobin of 8.6 gm/dl, reticulocyte count of 16.2%, RBC morphology normal, and platelet count 40,000/mm.^{3} The serum bilirubin was 1.7 mg/dl total, the total protein 4.3 gm/dl, the blood type A-Rh positive, and direct Coombs negative. A KUB demonstrated multiple loops of distended bowel with massive ascites. No intraperitoneal calcifications were noted. An abdominal paracentesis was performed for the relief of respiratory compromise and diagnosis. Approximately 120 cc of brown fluid were obtained.

At laparotomy there was meconium peritonitis with perforation, volvulus, and atresia of the distal ileum. The necrotic distal ileum and a 10 cm duplication of the small intestine were resected. Postoperatively the hemoglobin stabilized and the reticulocyte count fell to normal values. A TORCH screen and hemolytic workup were negative. She died at 7 months of age. At postmortem examination there were no other congenital anomalies.

While hydramnios may occur in up to 1 to 2% of all pregnancies, acute hydramnios is uncommon. It is often associated with uniovular twin pregnancy. When found in singleton pregnancies it is frequently associated with concealed intrapartum hemorrhage or fetal congenital anomalies. Gastrointestinal obstruction is second only to anencephaly as a fetal anomaly resulting in hydramnios.[2]

Amniocentesis has been advocated in the management and diagnosis of acute hydramnios. Liley[1] noted that the 450 μm absorption peak of amniotic fluid may be enlarged misleadingly by contamination with the heavily pigmented serum of an affected fetus, by the presence of meconium, or by the regurgitation of bile in the case of obstruction of the alimentary tract distal to the papilla of Vater.

Intestinal atresia has been diagnosed in utero by the

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use of amniofetography. The injection of iodide-containing dyes into the amniotic fluid may not be without risk to fetal thyroid function.[3] A method for the determination of bile acid concentration in the amniotic fluid has been described.[4] The measurement of these bile acids may be a useful diagnostic procedure in the evaluation of patients with hydramnios and would permit the prenatal diagnosis of intestinal obstruction distal to the papilla of Vater.

In the case presented, both the obstetrician and the pediatrician were led to believe that the high elevation of the spectral absorption curve was due to a hemolytic process. The subsequent finding of intra-abdominal hemorrhage, a negative hemolytic evaluation, and the lack of a rapid rise in serum bilirubin are all factors which negate the diagnosis of a hemolytic disorder. The elevated reticulocyte count and low hemoglobin, secondary to intra-abdominal hemorrhage, remained normal after postoperative blood replacement. These findings are in agreement with the conclusion of an acute intra-abdominal catastrophe in utero resulting in acute hydramnios with regurgitation of bile into the amniotic fluid.

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Pediatric and Adolescent Gynecology

The Department of Obstetrics and Gynecology and The Page and William Black Post-Graduate School of Medicine of the Mount Sinai School of Medicine (City University of New York) announce a postgraduate course, "Pediatric and Adolescent Gynecology, under the Direction of Albert Altchek, M.D., with guest faculty and faculty of the Mount Sinai School of Medicine, to be presented June 7 and 8, 1979, 9:00 AM to 5:00 PM (two sessions).

Apply to: Director, The Page and William Black Post-Graduate School of Medicine, Mount Sinai School of Medicine, One Gustave L. Levy Place, New York, New York 10029. Telephone: (212) 650-6737.

IUD and Biodegradable Delivery Systems

An international symposium, "IUD and Biodegradable Delivery Systems" will be held in Amsterdam, Holland, June 28-30, 1979. Program Directors are W. van Os, Haarlem, Holland, and E. S. E. Hafez, Detroit, Michigan. For information contact: Symposium Office, Miss K. Spanjaard, P. O. Box 20, 5340 Oss, Holland, Telex: 50959.

Seventh Annual Breastfeeding Seminar for Physicians

The Seventh Annual Breastfeeding Seminar for Physicians, sponsored by La Leche League International, will be held on July 6, 1979, at The Atlanta Hilton, Atlanta, Georgia, from 9:00 A.M. to 4:30 P.M.

For further information contact: Carol Kolar, R.N., Coordinator, Continuing Medical Education, La Leche League International, 9616 Minneapolis Ave., Franklin Park, Illinois 60131.

Bioethics and Public Policy

The Institute of Society, Ethics and the Life Sciences will sponsor a workshop this summer on "Bioethics and Public Policy," which will be held at the University of Colorado in Boulder, Colorado, from July 15 through 22, 1979.

For information contact: The Hastings Center, 360 Broadway, Hastings-on-Hudson, New York, 10706. Telephone: (914) 478-0500.

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While every precaution is taken to insure accuracy, we cannot guarantee against the possibility of an occasional change or omission in the preparation of this index.

BELLERGAL-S™ TABLETS

Composition: Each Bellergal-S Tablet contains: phenobarbital, USP, central sedative (Warning: May be habit forming), 40.0 mg; Gynergen (ergotamine tartrate, USP) sympathetic inhibitor, 0.6 mg; Bellafoline (levorotatory alkaloids of belladonna, as malates) parasympathetic inhibitor, 0.2 mg.

Properties and Therapeutics: Based on the concept that functional disorders frequently involve hyperactivity of both the sympathetic and parasympathetic nervous systems, the ingredients in Bellergal are combined to provide a balanced preparation designed to correct imbalance of the autonomic nervous system. The integrated action of Bellergal is effected through the combined administration of ergotamine and the levorotatory alkaloids of belladonna, specific inhibitors of the sympathetic and parasympathetic respectively, reinforced by the synergistic action of phenobarbital in dampening the cortical centers.

Indications: Bellergal is employed in the management of disorders characterized by nervous tension and exaggerated autonomic response:

Menopausal disorders with hot flashes, sweats, restlessness and insomnia.

Cardiovascular disorders with palpitation, tachycardia, chest oppression and vasomotor disturbances.

Gastrointestinal disorders with hypermotility, hypersecretion, "nervous stomach," and alternately diarrhea and constipation.

Genitourinary—uterine cramps, etc.

Premenstrual tension.

Interval treatment of *recurrent, throbbing headache.*

Contraindications: Peripheral vascular disease, coronary heart disease, hypertension, impaired hepatic or renal function, sepsis, third trimester of pregnancy and glaucoma. Hypersensitivity to any of the components.

Precautions: Even though the ergotamine tartrate content of this product is extremely low and untoward effects have been rare and insignificant, caution should be exercised if large or prolonged dosage is contemplated, and physicians should be alert to possible peripheral vascular complications in patients highly sensitive to ergot. Due to presence of a barbiturate, may be habit forming.

Side Effects: Blurred vision, dry mouth, flushing, drowsiness occur rarely.

Dosage: Bellergal-S Tablets: One in the morning and one in the evening.

How Supplied: Bellergal-S Tablets (compressed, scored tablets of tricolored pattern: dark green, orange and light lemon yellow) in bottles of 100.

Dorsey LABORATORIES
Division of Sandoz, Inc.
LINCOLN, NEBRASKA 68501

NONHORMONAL therapy for menopausal vasomotor instability is receiving renewed attention.

BELLERGAL-S™

TABLETS

Each Bellergal-S Tablet contains: phenobarbital, USP, central sedative (Warning: May be habit forming), 40.0 mg; Gynergen® (ergotamine tartrate, USP) sympathetic inhibitor, 0.6 mg; Bellafoline® (levorotatory alkaloids of belladonna, as malates) parasympathetic inhibitor, 0.2 mg.



Long clinical experience has established the effectiveness of Bellergal-S Tablets in managing menopausal disorders characterized by exaggerated autonomic response—hot flashes, sweats, restlessness, and insomnia.

Because Bellergal-S reduces autonomic nervous system activity, symptoms of vasomotor instability are eliminated or significantly reduced. *Bellergal-S does not contain estrogen in any form.* That's one reason why it is receiving renewed attention from physicians who wish to avoid the potential complications of estrogen therapy in vasomotor instability.

So when estrogen therapy is undesirable... prescribe Bellergal-S Tablets.

Please see prescribing information on an adjoining page.

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May 15, 1979
volume 134, *number* 2

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Why the choice is Cu-7®

intrauterine copper contraceptive.





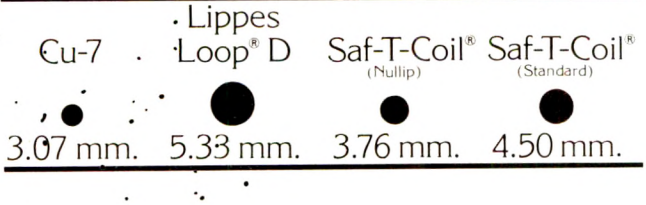




1. She wants nonhormonal contraception.
2. She wants to space her family.
3. She smokes.
4. She has passed the "Pill" years.

Freedom—intrauterine contraception is the most convenient of all contraceptive methods.

Comfort—smallest inserter diameter of all IUDs. This means minimal discomfort during insertion.



Security—high efficacy and relatively low incidence of expulsion and medical removal.

(Rates—based on labeling claims—expressed as events per 100 women through 12 months of use for parous women)[1]	Cu-7[1]	Lippes Loop D[2]	Saf-T-Coil[2]
Pregnancy	1.9	2.7	2.4
Expulsion	5.7	12.7	18.3
Medical Removal	10.9	15.2	15.6

These rates are derived from separate studies conducted by different investigators in several population groups. Different rates have been reported from other clinical trials.

References: 1. Data on file at Searle Laboratories. 2. Physicians' Desk Reference, Medical Economics Company, Oradell, N.J., 1978, pp. 1216, 1521.

Intrauterine contraception is not appropriate for all women. Please see complete product information prior to use. A brief summary of product information appears on the next page

Description: The plastic component of the Cu-7 is composed of pharmaceutical grade polypropylene homopolymer with barium sulfate added to render it radiopaque. Its shape approximates the number 7. It is substantially smaller than previously available intrauterine devices; the vertical dimension measures 36 mm. and the horizontal, 26 mm.

Coiled around the vertical limb is a pure, virgin electrolytic copper wire providing approximately 200mm^2 of exposed copper surface area. A retrieval thread is fastened to the free end of the vertical limb of the Cu-7.

The Cu-7 is supplied with a simple tubular polypropylene inserter. All components are sterile.

Mode of Action: Available data indicate that the contraceptive effectiveness of the Cu-7 is enhanced by a minute quantity of copper released continuously from the coiled copper into the uterine cavity.

The exact mechanism by which metallic copper enhances the contraceptive effect of an IUD has not been conclusively demonstrated. Various hypotheses have been advanced, the most common being that copper placed in the uterus interferes with enzymatic or other processes that regulate blastocyst implantation.

Animal studies suggest that copper may play an additional role by reduction of sperm transport within the uterine environment.

Indication and Usage: The Cu-7 is indicated for contraception.

Contraindications: The Cu-7 should not be inserted when any of the following conditions exist: pregnancy or suspicion of pregnancy; abnormalities of the uterus resulting in distortion of the uterine cavity; acute pelvic inflammatory disease or a history of repeated pelvic inflammatory disease; postpartum endometritis or infected abortion in the past three months; known or suspected uterine or cervical disease such as hyperplasia or carcinoma including unresolved, abnormal "Pap" smear; vaginal bleeding of unknown etiology; untreated acute cervicitis until infection is controlled; diagnosed Wilson's disease; known or suspected allergy to copper; previous ectopic pregnancy, and significant anemia.

Warnings

1. Pregnancy: (a) Long-term effects. The long-term effects on the offspring of the presence of copper in the uterus when pregnancy occurs with the Cu-7 are unknown.

(b) Septic abortion. Reports have indicated an increased incidence of septic abortion associated in some instances with septicemia, septic shock and death in patients becoming pregnant with an IUD in place. Most of these reports have been associated with the mid-trimester of pregnancy. In some cases, the initial symptoms have been insidious and not easily recognized. If pregnancy should occur with a Cu-7 in situ, the Cu-7 should be removed if the thread is visible or, if removal proves to be or would be difficult, interruption of the pregnancy should be considered and offered to the patient as an option, bearing in mind that the risks associated with an elective abortion increase with gestational age.

(c) Continuation of pregnancy. If the patient chooses to continue the pregnancy and the Cu-7 remains in situ, she must be warned of the increased risk of spontaneous abortion and the increased risk of sepsis, including death. The patient must be closely observed and she must be advised to report immediately all abnormal symptoms, such as flu-like syndrome, fever, abdominal cramping and pain, bleeding, or vaginal discharge, because generalized symptoms of septicemia may be insidious.

2. Ectopic pregnancy: (a) A pregnancy which occurs with an IUD in situ is more likely to be ectopic than a pregnancy occurring without an IUD. Therefore, patients who become pregnant while using a Cu-7 should be carefully evaluated for the possibility of an ectopic pregnancy.

(b) Special attention should be directed to patients with delayed menses, slight metrorrhagia and/or unilateral pelvic pain, and to those patients who wish to interrupt a pregnancy occurring in the presence of a Cu-7, to determine whether ectopic pregnancy has occurred.

3. Pelvic infection. An increased risk of pelvic inflammatory disease associated with the use of IUDs has been reported. While unconfirmed, this risk appears to be greatest for young women who are nulliparous and/or who have a multiplicity of sexual partners. Salpingitis can result in tubal damage and occlusion, thereby threatening future fertility. Therefore, it is recommended that patients be taught to look for symptoms of pelvic inflammatory disease. The decision to use an IUD in a particular case must be made by the physician and patient with the consideration of a possible deleterious effect on future fertility.

Pelvic infection may occur with a Cu-7 in situ and at times result in the development of tubo-ovarian abscesses or general peritonitis. The symptoms of pelvic infection include: new development of menstrual disorders (prolonged or heavy bleeding), abnormal vaginal discharge, abdominal or pelvic pain, dyspareunia, fever. The symptoms are especially significant if they occur following the first two or three cycles after insertion. Appropriate aerobic and anaerobic bacteriologic studies should be done and antibiotic therapy initiated promptly. If the infection does not show marked clinical improvement within 24 to 48 hours, the Cu-7 should be removed and the continuing treatment reassessed on the basis of the results of culture and sensitivity tests.

4. Embedment. Partial penetration or lodging of the Cu-7 in the endometrium or myometrium can result in a difficult removal. This may occur more frequently in smaller uteri. (See removal instructions.)

5. Perforation. Partial or total perforation of the uterine wall or cervix may occur with the use of the Cu-7, usually during insertions into patients sooner than two months after abortion or delivery or in uterine cavities too small for the Cu-7. The possibility of perforation must be kept in mind during insertion and at the time of any subsequent examination. If perforation occurs, laparotomy or laparoscopy should be performed as soon as medically feasible and the Cu-7 removed. Abdominal adhesions, intestinal penetration, intestinal obstruction, and local inflammatory reaction with abscess formation and erosion of adjacent viscera may result if the Cu-7 is left in the peritoneal cavity.

6. Medical diathermy. The use of medical diathermy (short-wave and microwave) in a patient with a metal-containing IUD may cause heat injury to the surrounding tissue. Therefore, medical diathermy to the abdominal and sacral areas should not be used on patients using a Cu-7.

7. Effects of copper. Additional amounts of copper available to the body from the Cu-7 may precipitate symptoms in women with undiagnosed Wilson's disease. The incidence of Wilson's disease is 1 in 200,000.

Precautions

1. Patient counseling. Prior to the insertion the physician, nurse, or other trained health professional must provide the patient with the Patient Brochure. The patient should be given the opportunity to read the brochure and discuss fully any questions she may have concerning the Cu-7 as well as other methods of contraception.

2. Patient evaluation and clinical considerations: a) A complete medical history should be obtained to determine conditions that might influence the selection of an IUD. A physical examination should include a pelvic examination, "Pap" smear, gonorrhea culture and, if indicated, appropriate tests for other forms of venereal disease. The physician should determine that the patient is not pregnant.

(b) The uterus should be carefully sounded prior to the insertion to determine the degree of patency of the endocervical canal and the internal os, and the direction and depth of the uterine cavity. Exercise care to avoid perforation with the sound. DO NOT USE THE Cu-7 INSERTION INSTRUMENT AS A SOUND. In occasional cases, severe cervical stenosis may be encountered. Do not use excessive force to overcome this resistance.

(c) The uterus usually sounds to a depth of 6 to 8 cm. Insertion of a Cu-7 into a uterine cavity measuring less than 6.5 cm. by sounding may increase the incidence of pain, bleeding, partial or complete expulsion, perforation, and possibly pregnancy.

(d) To reduce the possibility of insertion in the presence of an existing undetermined pregnancy, the optimal time for insertion is the latter part of the menstrual flow or one or two days thereafter. The Cu-7 should not be inserted post partum or post abortion until involution of the uterus is complete. The incidence of perforation and expulsion is greater if involution is not complete.

It is, however, necessary to place the Cu-7 as high as possible within the uterine cavity to help avoid partial or complete expulsion that could result in pregnancy.

Since the Cu-7 represents a different design in intrauterine contraception, physicians are cautioned that it is imperative for them to become thoroughly familiar with the instructions for use before attempting placement of the Cu-7.

(e) IUDs should be used with caution in those patients who have an anemia or a history of menorrhagia or hypermenorrhea. Patients experiencing menorrhagia and/or metrorrhagia following IUD insertion may be at risk for the development of hypochromic microcytic anemia. Also, IUDs should be used with caution in patients receiving anticoagulants or having a coagulopathy.

(f) Syncope, bradycardia or other neurovascular episodes may occur during insertion or removal of IUDs, especially in patients with a previous disposition to these conditions.

(g) Patients with valvular or congenital heart disease are more prone to develop subacute bacterial endocarditis than patients who do not have valvular or congenital heart disease. Use of an IUD in these patients may represent a potential source of septic emboli.

(h) Use of an IUD in those patients with acute cervicitis should be postponed until proper treatment has cleared up the infection.

(i) Since the Cu-7 may be partially or completely expelled, patients should be reexamined and evaluated shortly after the first postinsertion menses, but definitely within three months after insertion. Thereafter annual examination with appropriate medical and laboratory evaluation should be carried out. The Cu-7 should be replaced every three years.

(j) The patient should be told that some bleeding or cramps may occur during the first few weeks after insertion, but if these symptoms continue or are severe she should report them to her physician. She should be instructed on how to check after each menstrual period to make certain that the thread still protrudes from the cervix and cautioned that there is no contraceptive protection if the Cu-7 has been expelled. She should also be cautioned not to dislodge the Cu-7 by pulling on the thread. If a partial expulsion occurs, removal is indicated and a new Cu-7 may be inserted. The patient should be told to return within three years for removal of the Cu-7 and for replacement if desired.

(k) A copper-induced urticarial allergic skin reaction may develop in women using a copper-containing IUD. If symptoms of such an allergic response occur, the patient should be instructed to tell the consulting physician that a copper-containing device is being used.

(l) The Cu-7 should be removed for the following medical reasons: menorrhagia and/or metrorrhagia producing significant anemia; uncontrolled pelvic infection; intractable pain often aggravated by intercourse, dyspareunia; pregnancy, if the thread is visible; endometrial or cervical malignancy; uterine or cervical perforation; or any indication of partial expulsion.

(m) If the retrieval thread cannot be visualized it may have retracted into the uterus or have been broken off, or the Cu-7 may have been expelled. Localization usually may be made by feeling with a probe; if not, x-ray or sonography can be used. When the physician elects to recover a Cu-7 with the thread not visible, the removal instructions should be considered.

(n) If any patient with a Cu-7 suddenly develops overt clinical hepatitis or abnormal liver function tests, appropriate diagnostic procedures should be initiated.

Adverse Reactions: Perforations of uterus and cervix have occurred. Perforation into the abdomen has been followed by abdominal adhesions, intestinal penetration, intestinal obstruction, local inflammatory reaction with abscess formation and erosion of adjacent viscera. Pregnancy has occurred with the Cu-7 in situ and when the Cu-7 has been partially or completely expelled.

The incidence of spontaneous abortion, when conception occurs with intrauterine devices in situ, appears to be increased over that in unprotected women. Insertion cramping, usually of no more than a few seconds duration, may occur; however, some women may experience residual cramping for several hours or even days. Intermenstrual spotting or bleeding or prolonged or increased menstrual flow may occur.

Pelvic infection including salpingitis with tubal damage or occlusion has been reported. This may result in future infertility. Complete or partial expulsion of the Cu-7 may sometimes occur, particularly in those patients with uteri measuring less than 6.5 cm. by sounding. Urticarial allergic skin reaction may occur. The following complaints have also been reported with IUDs although their relation to the Cu-7 has not been established: amenorrhea or delayed menses, backaches, cervical erosion, cystic masses in the pelvis, vaginitis, leg pain or soreness, weight loss or gain, nervousness, dyspareunia, cystitis, endometritis, septic abortion, septicemia, leukorrhea, ectopic pregnancy, difficult removal, uterine embedment, anemia, pain, neurovascular episodes including bradycardia and syncope secondary to insertion, dysmenorrhea, and fragmentation of the IUD.

Directions for Use: The Cu-7 is to be placed within the uterine cavity. See the Procedure for Insertion for two insertion techniques.

The small diameter of the Cu-7 facilitates easy insertion in nulligravidous and nulliparous, as well as parous women. The optimal time of insertion is during the latter part of the menstrual flow or one or two days thereafter. The cervical canal is relatively more patent at this time, and there is little chance that the patient may be pregnant.

Present information indicates that efficacy is retained for 36 months. There is no evidence that contraceptive efficacy decreases with time up to three years of use, but until adequate data indicating a longer effective life become available, the Cu-7 must be removed within 36 months from the date of insertion and a new one inserted if desired. If partial expulsion occurs, removal is indicated, and a new Cu-7 may be inserted. Removal of the Cu-7 may also be indicated in the event of heavy or persistent bleeding.

The physician should become thoroughly familiar with the instructions for use before attempting insertion or removal of the Cu-7.

Clinical Efficacy: In clinical trials of the Cu-7 conducted by Searle Laboratories, use effectiveness was determined as follows for parous and nulliparous women, as tabulated by the life table method. (Rates are expressed as cumulative events per 100 women through 12, 24, and 36 months of use.)

This experience encompasses 387,131 woman-months of use, including 12 months for 11,517 women, 24 months for 7,895, and 36 months for 3,661.

	12 Months		24 Months		36 Months	
	Parous	Nulliparous	Parous	Nulliparous	Parous	Nulliparous
Pregnancy	1.9	1.7	2.9	2.6	3.4	3.4

How Supplied

Available in cartons of 6, 30 and 100 sterile units (Cu-7 with an inserter) and sufficient patient leaflets and identification cards.

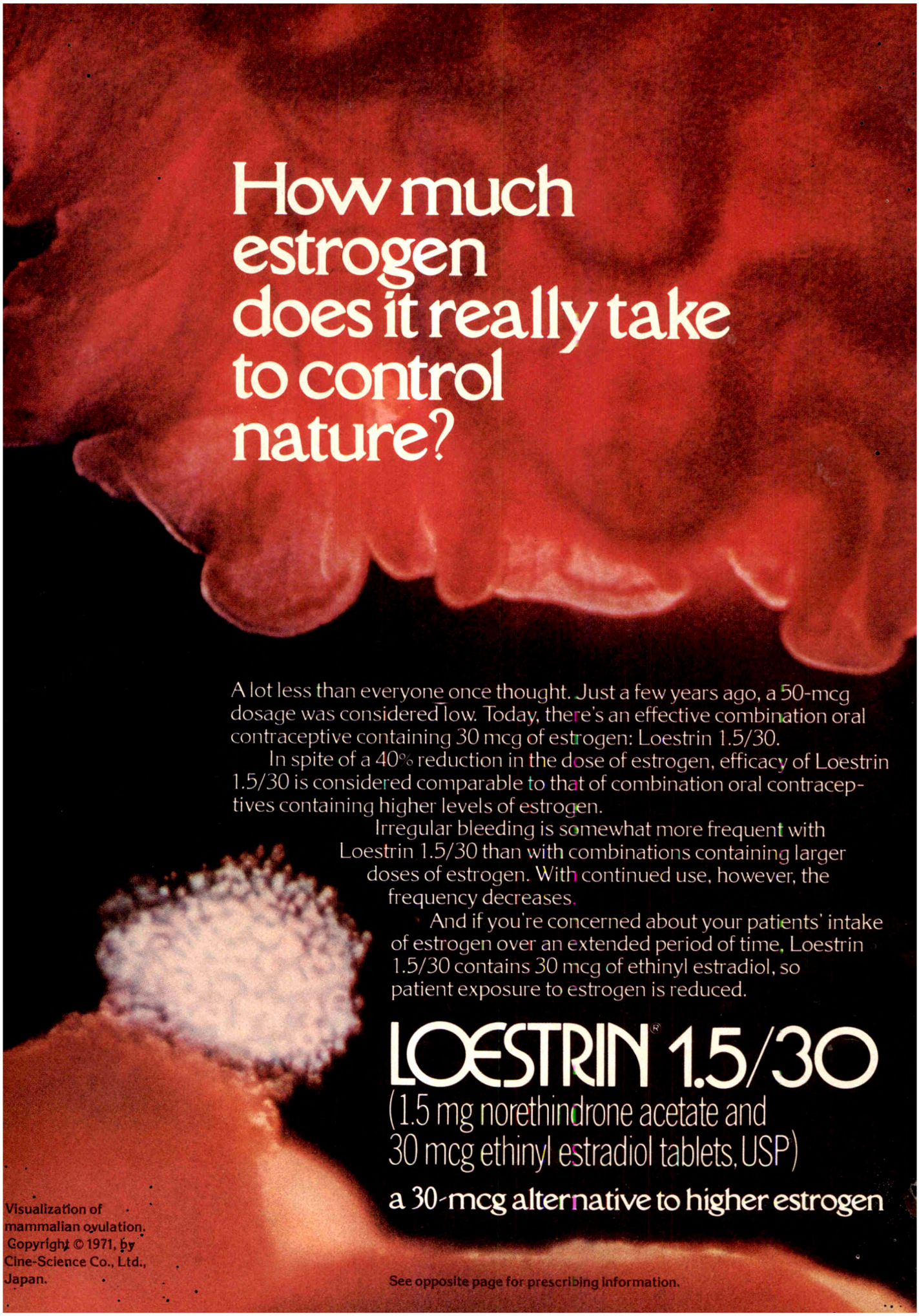
Please see complete product labeling for additional information, including insertion and removal instructions.

SEARLE **Searle Laboratories**
Division of Searle Pharmaceuticals Inc.
Box 5110, Chicago, Illinois 60680

Cu-7® intrauterine copper contraceptive

—the leading IUD

8B4


How much estrogen does it really take to control nature?
A lot less than everyone once thought. Just a few years ago, a 50-mcg dosage was considered low. Today, there's an effective combination oral contraceptive containing 30 mcg of estrogen: Loestrin 1.5/30.
In spite of a 40% reduction in the dose of estrogen, efficacy of Loestrin 1.5/30 is considered comparable to that of combination oral contraceptives containing higher levels of estrogen.
Irregular bleeding is somewhat more frequent with Loestrin 1.5/30 than with combinations containing larger doses of estrogen. With continued use, however, the frequency decreases.
And if you're concerned about your patients' intake of estrogen over an extended period of time, Loestrin 1.5/30 contains 30 mcg of ethinyl estradiol, so patient exposure to estrogen is reduced.
LOESTRIN® 1.5/30
(1.5 mg norethindrone acetate and 30 mcg ethinyl estradiol tablets, USP)
a 30-mcg alternative to higher estrogen
Visualization of mammalian ovulation. Copyright © 1971, by Cine-Science Co., Ltd., Japan.
See opposite page for prescribing information.

Brief Summary of Prescribing Information
LOESTRIN® 1.5/30
(1.5 mg norethindrone acetate and 30 mcg ethinyl estradiol tablets, USP) See section under Special Notes on Administration and How Supplied.

DESCRIPTION
Loestrin 1.5/30 Products are progestogen-estrogen combinations.

INDICATION AND USAGE
Loestrin 1.5/30 Products are indicated for the prevention of pregnancy in women who elect to use oral contraceptives.

In clinical trials with Loestrin 1.5/30 involving 17,139 therapy cycles, there was a pregnancy rate of 0.49 per 100 woman years.

Dose-related risk of thromboembolism from oral contraceptives: Studies have shown a positive association between the dose of estrogens in oral contraceptives and the risk of thromboembolism. It is prudent and in keeping with good principles of therapeutics to minimize exposure to estrogen. The oral contraceptive prescribed for any given patient should be that product which contains the least amount of estrogen that is compatible with an acceptable pregnancy rate and patient acceptance.

CONTRAINDICATIONS
1. Thrombophlebitis or thromboembolic disorders
2. A past history of deep-vein thrombophlebitis or thromboembolic disorders
3. Cerebral vascular or coronary artery disease
4. Known or suspected carcinoma of the breast
5. Known or suspected estrogen-dependent neoplasia
6. Undiagnosed abnormal genital bleeding
7. Known or suspected pregnancy (See No. 5 under WARNINGS.)

WARNINGS

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

The use of oral contraceptives is associated with increased risk of several serious conditions including thromboembolism, stroke, myocardial infarction, hepatic adenoma, gallbladder disease, and hypertension. Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks.

1. *Thromboembolic Disorders and Other Vascular Problems:* An increased risk of thromboembolic and thrombotic disease associated with the use of oral contraceptives is well-established. Studies have demonstrated an increased risk of fatal and nonfatal venous thromboembolism and stroke, both hemorrhagic and thrombotic.

Cerebrovascular disorders: In a collaborative study in women with and without predisposing causes, it was estimated that the risk of hemorrhagic stroke was 2.0 times greater in users than nonusers, and the risk of thrombotic stroke was 4.0 to 9.5 times greater.

Myocardial infarction: An increased risk of myocardial infarction associated with oral contraceptives has been reported confirming a previously suspected association. These studies found that the greater the number of underlying risk factors (cigarette smoking, hypertension, hypercholesterolemia, obesity, diabetes, history of preeclamptic toxemia) for coronary artery disease, the higher the risk of developing myocardial infarction, regardless of whether the patient was an oral contraceptive user or not. Oral contraceptives, however, were found to be a clear additional risk factor.

It has been estimated that users who do not smoke (smoking is considered a major predisposing condition to myocardial infarction) are about twice as likely to have a fatal myocardial infarction as nonusers who do not smoke. Oral contraceptive users who are smokers have about a fivefold increased risk of fatal infarction compared to users who do not smoke, but about a tenfold to twelvefold increased risk compared to nonusers who do not smoke. The amount of smoking is also an important factor.

Risk of dose: In an analysis of data, British investigators concluded that the risk of thromboembolism including coronary thrombosis is directly related to the dose of estrogen used in oral contraceptives; however, the quantity of estrogen may not be the sole factor involved.

Estimate of excess mortality from circulatory diseases: The risk of diseases of the circulatory system is concentrated in older women, in those with a long duration of use, and in cigarette smokers.

A study of available data from a variety of sources concluded that the mortality associated with all methods of birth control is low and below that associated with childbirth, with the exception of oral contraceptives in women over 40 who smoke.

The risk of thromboembolic and thrombotic diseases associated with oral contraceptives increases with age after approximately age 30 and, for myocardial infarction, is further increased by hypertension, hypercholesterolemia, obesity, diabetes, or history of preeclamptic toxemia, and especially by cigarette smoking.

The physician and the patient should be alert to the earliest manifestations of thromboembolic and thrombotic disorders. Should any occur or be suspected, the drug should be discontinued immediately.

A fourfold to sixfold increased risk of postsurgery thromboembolic complications has been reported in users. If feasible, oral contraceptives should be discontinued at least four weeks before surgery of a type associated with an increased risk of thromboembolism or prolonged immobilization.

2. *Ocular lesions:* Neuro-ocular lesions, such as optic neuritis or retinal thrombosis, have been associated with the use of oral contraceptives. Discontinue the oral contracept ve if there is unexplained sudden or gradual, partial, or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal vascular lesions.

3. *Carcinoma:* Long-term continuous administration of estrogen in certain animal species increases the frequency of carcinoma of the breast, cervix, vagina, and liver.

In humans, an increased risk of endometrial carcinoma associated with the prolonged use of exogenous estrogen in postmenopausal women has been reported. However, there is no evidence suggesting increased risk of endometrial cancer in users of conventional combination or progestogen-only oral contraceptives.

Studies found no evidence of increase in breast cancer in women taking oral contraceptives; however, an excess risk in users with documented benign breast disease was reported.

There is no confirmed evidence of an increased risk of cancer associated with oral contraceptives. Close clinical surveillance of users is, nevertheless, essential. In cases of undiagnosed persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be taken to rule out malignancy. Women with a strong family history of breast cancer, or who have breast nodules, fibrocystic disease, or abnormal mammograms, should be monitored with particular care.

4. *Hepatic Tumors:* Benign hepatic adenomas have been found to be associated with oral contraceptives. Because hepatic adenomas may rupture and may cause death through intra-abdominal hemorrhage, they should be considered in women presenting abdominal pain and tenderness, abdominal mass, or shock.

A few cases of hepatocellular carcinoma have been reported in women taking oral contraceptives. The relationship of these drugs to this type of malignancy is not known at this time.

5. *Usage in or Immediately Preceding Pregnancy; Birth Defects in Offspring, and Malignancy in Female Offspring:* During early pregnancy, female sex hormones may seriously damage the offspring.

An increased risk of congenital anomalies, including heart defects and limb defects, has been reported with the use of oral contraceptives in pregnancy.

There is some evidence that triploidy and possibly other types of polyploidy are increased among abortuses from women who become pregnant soon after ceasing oral contraceptives.

Pregnancy should be ruled out before continuing an oral contraceptive in any patient who has missed two consecutive menstrual periods. If the patient has not adhered to the schedule, the possibility of pregnancy should be considered at the time of the first missed period, and oral contraceptives should be withheld until pregnancy has been ruled out. If pregnancy is confirmed, the patient should be apprised of the potential risks to the fetus and the advisability of continuation of the pregnancy should be discussed.

Women who discontinue oral contraceptives with the intent of becoming pregnant should use an alternate form of contraception for a period of time before attempting to conceive.

Administration of progestogen-only or progestogen-estrogen combinations to induce withdrawal bleeding should not be used as a test of pregnancy.

6. *Gallbladder Disease:* Studies report an increased risk of surgically confirmed gallbladder disease in users of oral contraceptives.

7. *Carbohydrate and Lipid Metabolic Effects:* Because decreased glucose tolerance has been observed in a significant percentage of patients, prediabetic and diabetic patients should be carefully observed while receiving oral contraceptives.

An increase in triglycerides and total phospholipids has been observed.

8. *Elevated Blood Pressure:* An increase in blood pressure has been reported in patients receiving oral contraceptives. The prevalence in users increases with longer exposure. Age is also strongly correlated with development of hypertension. Women who previously have had hypertension during pregnancy may be more likely to develop elevation of blood pressure.

9. *Headache:* Onset or exacerbation of migraine or development of headache of a new pattern which is recurrent, persistent, or severe, requires discontinuation of oral contraceptives.

10. *Bleeding Irregularities:* Breakthrough bleeding, spotting, and amenorrhea are frequent reasons for patients discontinuing oral contraceptives. In breakthrough bleeding, nonfunctional causes should be borne in mind. In undiagnosed abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy.

Women with a past history of oligomenorrhea or secondary amenorrhea, or young women without regular cycles should be advised that they may have a tendency to remain anovulatory or to become amenorrheic after discontinuation of oral contraceptives.

11. *Ectopic Pregnancy:* Ectopic as well as intrauterine pregnancy may occur in contraceptive failures.

12. *Breast Feeding:* Oral contraceptives may interfere with lactation. Furthermore, a small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs.

PRECAUTIONS
1. A complete medical and family history should be taken prior to the initiation of oral contraceptives. The pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen, and pelvic organs, including Papanicolaou smear and relevant laboratory tests. As a general rule, oral contraceptives should not be prescribed for longer than one year without another examination.
2. Preexisting uterine leiomyomata may increase in size.
3. Patients with a history of psychic depression should be carefully observed and the drug discontinued if depression recurs to a serious degree.
4. Oral contraceptives may cause fluid retention and should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated.
5. Patients with a past history of jaundice during pregnancy have an increased risk of recurrence of jaundice. If jaundice develops, the medication should be discontinued.
6. Steroid hormones may be poorly metabolized and should be administered with caution in patients with impaired liver function.
7. Users may have disturbances in normal tryptophan metabolism, which may result in a relative pyridoxine deficiency.
8. Serum folate levels may be depressed.
9. The pathologist should be advised of oral contraceptive therapy when relevant specimens are submitted.
10. Certain endocrine and liver function tests and blood components may be affected. (a) Increased sulfobromophthalein retention. (b) Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability. (c) Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone. (d) Decreased pregnanediol excretion. (e) Reduced response to metyrapone test.

Drug interactions: Reduced efficacy and increased incidence of breakthrough bleeding have been associated with concomitant use of rifampin and an association has been suggested with barbiturates, phenylbutazone, phenytoin sodium, and ampicillin.

ADVERSE REACTIONS
An increased risk of the following serious adverse reactions has been associated with oral contraceptives.

Thrombophlebitis; Pulmonary embolism; Coronary thrombosis; Cerebral thrombosis; Cerebral hemorrhage; Hypertension; Gallbladder disease; Benign hepatomas; Congenital anomalies.

There is evidence of an association between the following conditions and the use of oral contraceptives, although additional confirmatory studies are needed: Mesenteric thrombosis, Neuro-ocular lesions, eg, retinal thrombosis and optic neuritis.

The following adverse reactions have been reported in patients receiving oral contraceptives and are believed to be drug-related: Nausea and/or vomiting, usually the most common adverse reactions, occur in approximately 10 percent or less of patients during the first cycle. Other reactions, as a general rule, are seen much less frequently or only occasionally: gastrointestinal symptoms; breakthrough bleeding; spotting; change in menstrual flow; dysmenorrhea; amenorrhea during and after treatment; temporary infertility after discontinuance of treatment; edema; chloasma or melasma; breast changes; change in weight; change in cervical erosion and cervical secretion; possible diminution in lactation when given immediately post partum; cholestatic jaundice; migraine; increase in size of uterine leiomyomata; rash (allergic); mental depression; reduced tolerance to carbohydrates; vaginal candidiasis; change in corneal curvature; intolerance to contact lenses.

The following adverse reactions have been reported and the association has been neither confirmed nor refuted.

Premenstrual-like syndrome; cataracts; changes in libido; chorea; changes in appetite; cystitis-like syndrome; headache; nervousness; dizziness; hirsutism; loss of scalp hair; erythema multiforme; erythema nodosum; hemorrhagic eruption; vaginitis; porphyria.

Special Notes on Administration
Loestrin 21 1.5/30 (1.5 mg norethindrone acetate and 30 mcg ethinyl estradiol tablets, USP)—Menstruation usually begins two or three days, but may begin as late as the fourth or fifth day, after discontinuing medication.

Loestrin Fe 1.5/30—Menstruation usually begins two or three days, but may begin as late as the fourth or fifth day, after the brown ferrous fumarate tablets have been started.

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The physician should be alert to the fact that the irregular bleeding patterns could mask bleeding from organic cause, and appropriate diagnostic measures should be taken if the bleeding persists or continues after changing to a higher estrogen-content product.

After several months, bleeding may be reduced to a virtual absence; reduced flow may be a result of medication and not indicative of pregnancy.

HOW SUPPLIED
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[1] First Health and Nutrition Survey, HEW Pub. No. (HRA) 74-1219-1.

[2] Herbert, V.—Current Concepts in Nutrition 5. 79 (1977)

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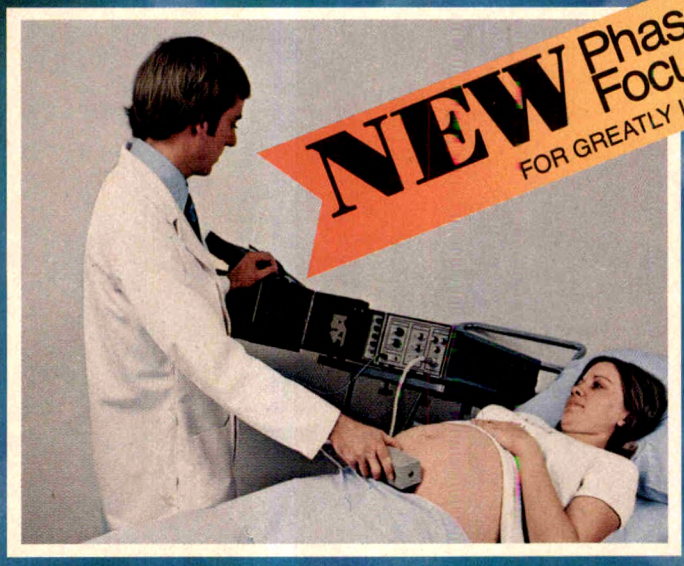
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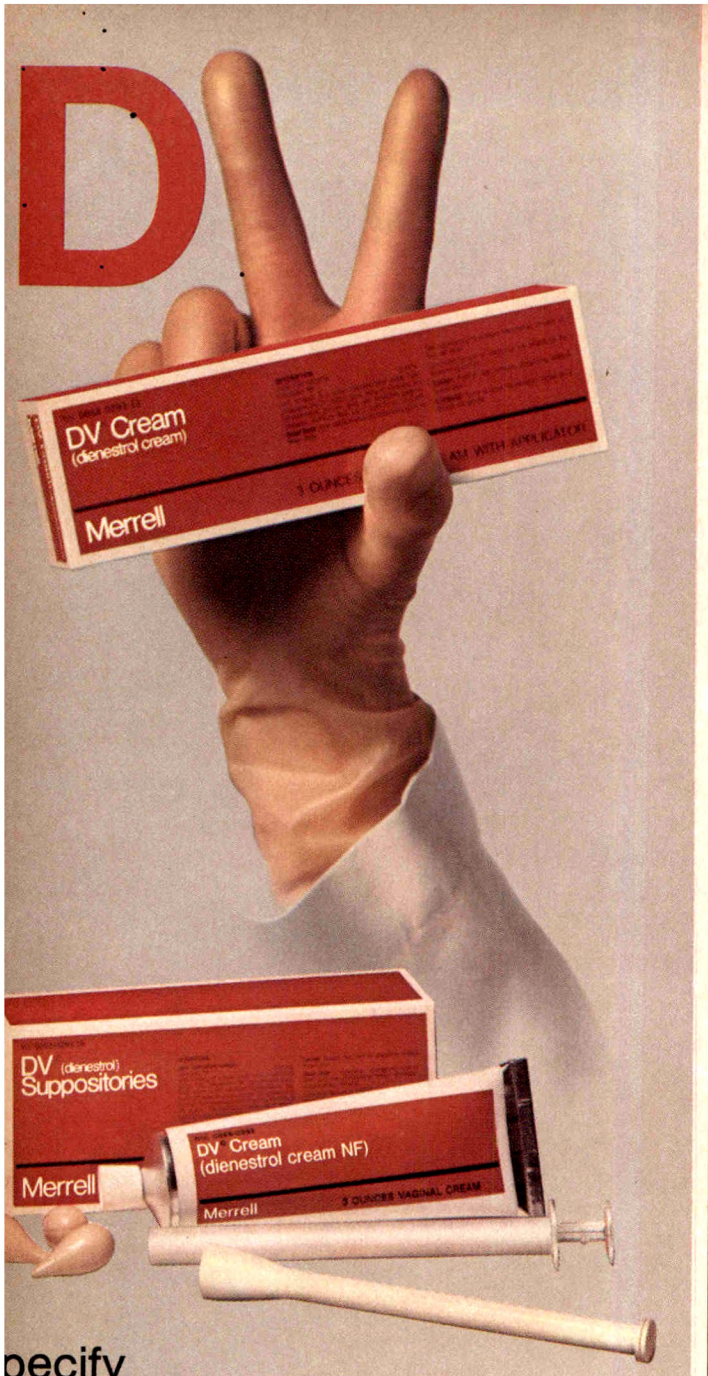
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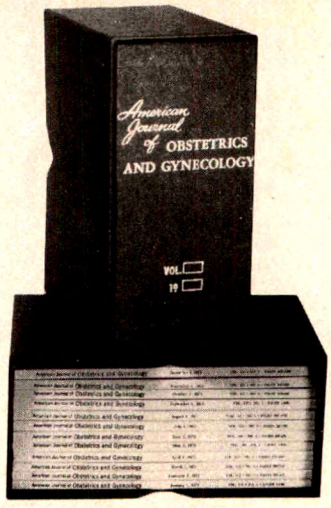
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PRECAUTIONS Head injury and increased intracranial pressure The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

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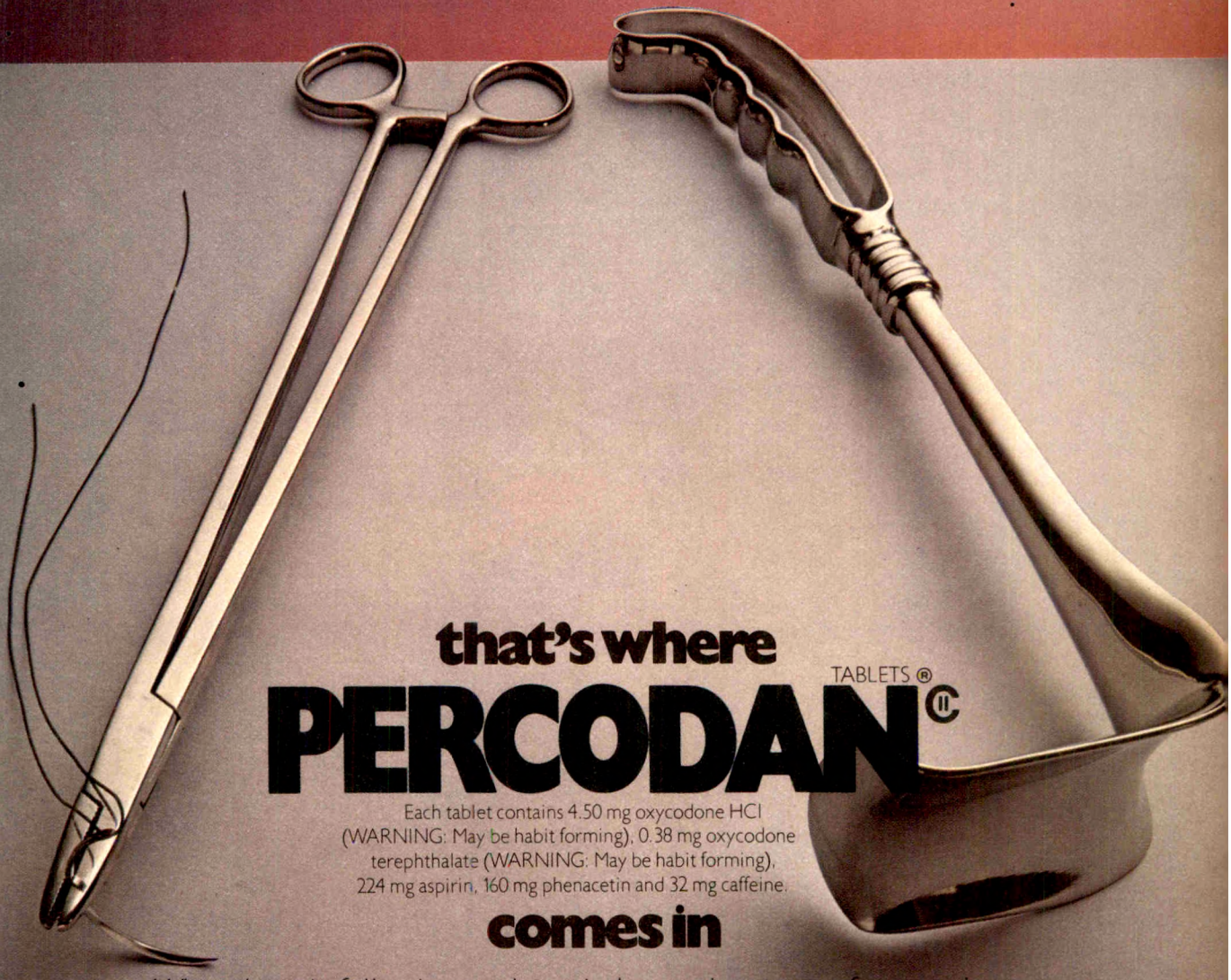
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Please see opposite page for brief summary of prescribing information.

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American Journal of Obstetrics and Gynecology

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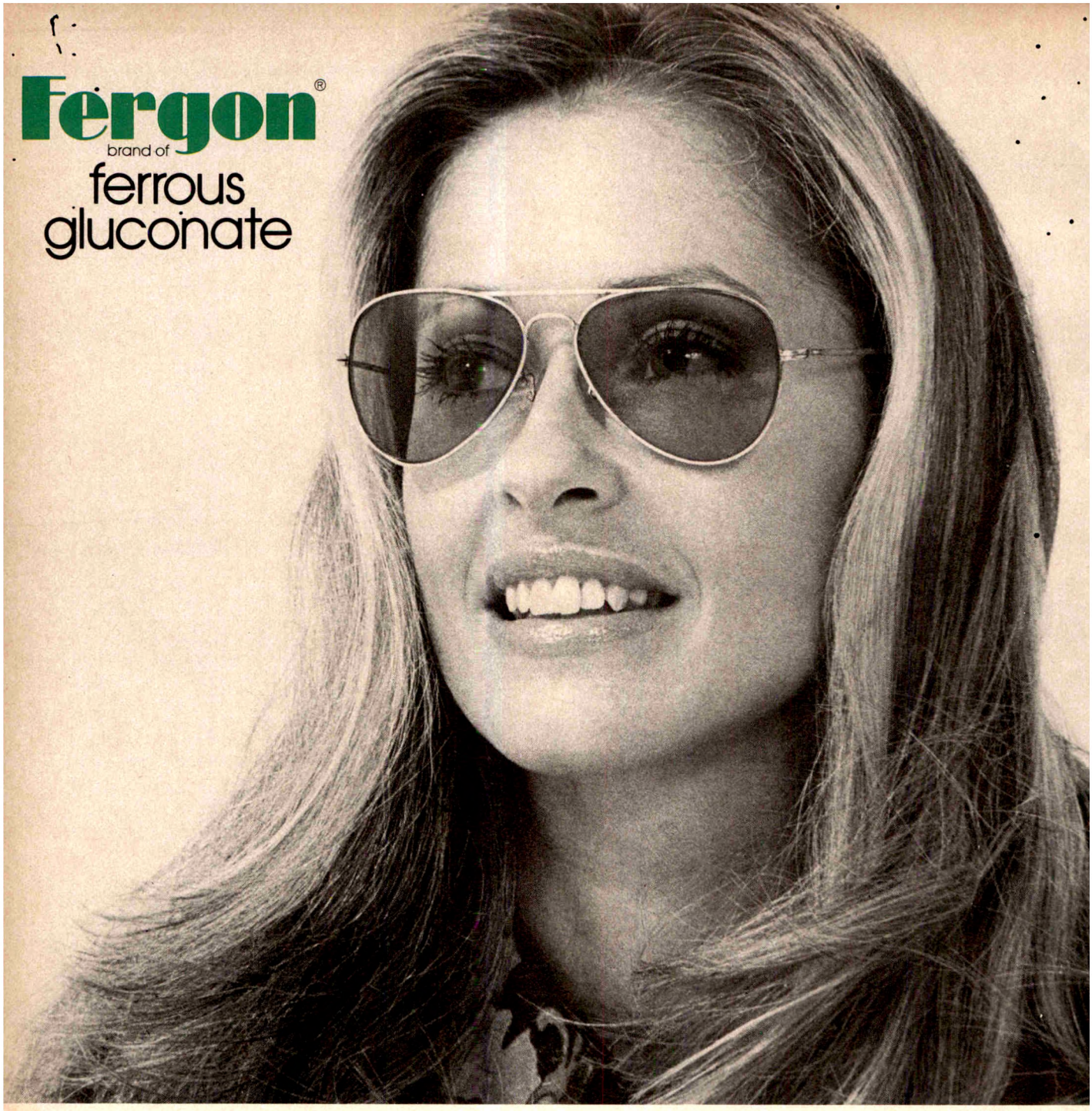
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American Journal of Obstetrics and Gynecology

volume 134 *number* 2 MAY 15, 1979

Transactions of the Forty-fifth Annual Meeting of the Pacific Coast Obstetrical and Gynecological Society

Our successors

Presidential address

WILLIAM J. DIGNAM, M.D.
Los Angeles, California

"SPEECHES ARE like babies—easy to conceive but hard to deliver" (anonymous) is an oft-repeated quotation, or as Smith[1] would have it: "Many physicians would prefer passing a small kidney stone to presenting a paper." I suppose that such concerns may well have application when one is addressing a group of strangers, and would-be critics, but they hardly apply to the presidential address of our society. Fortunately our society gives great latitude to its President regarding the type of address which is acceptable and it is, indeed, a great privilege and pleasure to be able to share a few thoughts with such a distinguished group of warm and loyal friends. I have chosen to comment upon the influences which are shaping the young gynecologists of our day, as I see them. I shall be brief, mindful of the warning of Southgate,[2] "Unfortunately, too many authors write as though they will never have another chance—and they are correct."

The laconic Smith[1] says, "There are many ways to deliver papers, the best way is to toss them on the front porch before sunup." I hope you will not share that feeling before I have finished.

One cannot, of course, escape a feeling of deep humility as he reflects upon the truly distinguished list of presidents who have preceded him to this podium, and one is tempted to borrow very heavily from the writings of these and other outstanding authors who are so facile with the written word.

No less a personage than Hippocrates (in his *Precepts*) has counseled us against quoting from the writings of others. "If for the sake of a crowded audience you do wish to hold a lecture, your ambition is no laudable one, and at least avoid all citations from the poets, for to quote them argues feeble industry." Feeble industry it may be indeed, but who of any judgment would not prefer the lilting phrases of the poets? I confess to a great fondness for such quotings. Who among us could phrase a recommendation for another physician so entertainingly as Auden?

> Give me a doctor partridge—plump,
> Short in the leg and broad in the rump,
> An endomorph with gentle hands
> Who'll never make absurd demands
> That I abandon all my vices
> Nor pull a long face in a crisis,
> But with a twinkle in his eye
> Will tell me that I have to die
>
> *W. H. Auden*
> *Footnotes to Dr. Sheldon*

Yes, even the announcement of a fatal disease can be made much more bearable by the compassionate physician. The compassionate physician Dunn[3] has stated it

Presented at the Forty-fifth Annual Meeting of the Pacific Coast Obstetrical and Gynecological Society, Gleneden Beach, Oregon, September 26-30, 1978.

Reprint requests: Dr. William J. Dignam, Department of Obstetrics and Gynecology, University of California Los Angeles Medical Center, Los Angeles, California 90024.

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so well to this society: "But, to care for our patients with compassion and to give of ourselves as one human being to another is a gift of God that no computer invented can ever satisfy."

Are there influences at work which might deprive society of its compassionate physicians? I think that there are. The first is the selection of students to study medicine. This has been the subject of extensive commentary and the cause of personal grievance for many a family, including many a physician's family. How often have we known a superb young man or woman who would clearly make a superb and compassionate young physician, only to find that some several apparently whimsical admissions committees have denied that student admission to medical school?

It is difficult to fault the admissions committees because few would deny that, "In diagnosing the illness of the sick, logic would dictate, physicians of high intellectual competence will be right more frequently than less talented physicians. Most of us in selecting our own physician will prefer a bright one to a dull one."[4]

The grade inflation extant in our colleges and universities today is well recognized. Thus a recent article in *The Atlantic Monthly* states: "Grade inflation is also epidemic. At Harvard, where one must assume resistance to this is greater than average, 85 percent of the class of 1977 graduated with honors, as compared with 39 percent of the class of 1957. Also, according to a recent report of the Harvard administration, 85 percent of all grades given there last year were B-minus or higher (compared with 70 percent in 1965-66)."*

Thus a typical medical school will be presented with 4,000 applicants for an entering class of 150 to 200 and at least 300 of them will have a grade point average of 3.7 or higher on their college transcripts. It is quite understandable that admissions committees feel that it is probably unnecessary to accept applicants with much below an A− average in order to admit a group of students who have appropriate personal characteristics *and* exceptional intelligence. These committees, however, must recognize that today applicants with high grade point averages do not necessarily have exceptional intelligence and that it is very difficult to appraise personal characteristics. Psychological testing for the selection of students has been tried and found wanting.

Certainly the interview system currently in vogue at many medical schools is not foolproof. Repeatedly students are admitted who are lacking in the personal characteristics necessary to permit them to function effectively in the clinical setting, not to mention those for whom the stresses are too great, and suicide results.

*From Chase, A.: Skipping through college The Atlantic Monthly, September, 1978, p. 34.

Not all medical students are destined for careers in *clinical* medicine and clearly the medical schools must provide opportunities for these individuals also, but present custom leaves the choice of field of endeavor to the individual, not to the institution, so that some individuals with superior intelligence but inadequate personal traits end up practicing clinical medicine.

One factor which makes the interview system difficult is the volume of applications which must be considered. Many of us have known single admissions officers who conducted the entire admissions process of a given school—judging personality traits by means of personal interview and evaluation of letters of recommendation. Many of these individuals had superb judgment. Now, however, the large volume of applicants virtually precludes this mechanism. Instead we have large committees and the variation in judgment among the members is introduced. It is a shame that the volume of applications has caused this situation because there are clearly a number of sterling individuals whose judgment and experience would qualify them very well to pick a medical school class. I should be delighted to have Dr. Dan Morton choose the entire generation of physicians to care for my children and their families and I know that he could do it single-handedly.

It may be that our society as an organization can have little influence on the selection of appropriate medical students, but certainly as individuals we can have an influence. Many groups and individuals associated with admissions committees show increasing interest in the selection of students with desirable personal characteristics and we can emphasize that attitude. Our letters of recommendation can be much more specific and avoid general platitudes. We can recruit appropriate students to the profession.

What of the attraction of well-motivated students to our specialty? Here we can have a major influence. It has become increasingly clear to me in interviewing residency applicants that one of the principal factors attracting students to obstetrics and gynecology, or to any other field for that matter, is the example of an instructor. Time and again I have heard: "I am attracted to obstetrics and gynecology because I noticed that Dr. X was so interested in his patients and they had such warm feelings towards him. It is not like some of the other specialties where a doctor does an excellent job technically, but then returns the patient to her referring physician and has no further interest in her. Obstetrics and gynecology has all the advantages of family practice but also has all the advantages of a specialty."

We can be even more considerate of these young

students as we see them in our offices and in our hospitals. Just a little time will often spark a developing interest.

I believe that our society could also encourage medical students by permitting or sponsoring a few of them to attend our meetings. Our society is unique and its spirit of fellowship is very warm and impressive. Students should be exposed to the joys of association with these compassionate physicians.

Again, the compassionate physician. So many of our patients require only that. They require a physician who is so compassionate that he will not saddle them with some arbitrary diagnosis when he is unable to discover the cause for their symptoms, or who will not contribute the necessary time to hear out a very anxious person. And yes, as Auden has suggested, some few of our patients must be escorted gracefully to their deaths. Even so somber a matter as dying can be made so much less somber by the poets.

> Die I must, but let me die drinking in an inn!
> Hold the wine-cup to my lips sparkling from the bin!
> So, when the angels flutter down to take me from my sin,
> "Ah, God have mercy on this sot," the cherubs will begin.
>
> *Walter De Map*

Who among us can raise the spirits of a patient so quickly and surely? Even the *Nonsense Verses* of Burgess remove us instantly from our daily cares.

> I'd rather have Fingers than Toes,
> I'd rather have Eyes than a Nose,
> And as for my Hair
> I'm glad it's all there,
> I'll be awfully sad when it goes.
>
> *Gelett Burgess*
> *Nonsense Verses*

> I never saw a Purple Cow,
> I never hope to see one;
> But I can tell you anyhow,
> I'd rather see than be one.
>
> *Gelett Burgess*
> *The Purple Cow*

> Ah, yes, I wrote the "Purple Cow"—
> I'm sorry, now, I wrote it!
> But I can tell you, anyhow,
> I'll kill you if you quote it.
>
> *Gelett Burgess*
> *Cinq Ans Après*

Hippocrates would have loved him—a poet who does not wish to be quoted.

What about our specialty? Will it be the same in the future if the compassionate young physicians are attracted into it? There are both external and internal influences which could produce some significant changes in their patterns of practice. Changes in patterns of practice may be very good if they result in better care for our patients. They can be very bad if the reverse is true.

Most of us feel that the development of the specialty of obstetrics and gynecology was a significant advance and that it has clearly resulted in better care for the female members of our population. A number of studies have indicated that women consider gynecologists as their personal physicians and turn to these gynecologists with *all* of their medical problems. However, better care will result only if gynecologists are informed about *all* of the problems and symptoms presented, and for the population as a whole, better care will result only if *all* women have access to suitable care.

A number of influences are at work and will have their effects on these considerations. With the elimination of the internship and the entry of the great majority of medical students into specialty training directly after medical school there is a clear possibility that our residents will be too narrowly trained unless we are very careful to include appropriate training within our residencies in obstetrics and gynecology. The American Board of Obstetrics and Gynecology[6] requirements state: "The candidate beginning graduate education in 1976 will be required to have completed not less than four years in approved clinical programs, with not less than 36 months of progressing responsibility for the care of obstetric and gynecologic patients, including the usual time as 'chief resident' in the program. Completion of a year of 'internship' plus a three year residency program will fulfill this requirement.

The Board recommends that the candidate intending to practice as an obstetrician and gynecologist spend a significant proportion of graduate education in a broadly oriented approach to patient care."[5]

Other influences would constantly narrow the field of activity of the obstetrician-gynecologist. Some come from outside the specialty and others from within the specialty.

Other groups of physicians see themselves as the logical individuals to care for some of our patients. For example, family practitioners are being trained to care for common gynecologic problems and normal obstetric problems, but the definitions of "common" and "normal" are inexact and "normal" may become "abnormal" quickly and unexpectedly. What of the second opinion? A consideration of hysterectomy for a patient with abnormal bleeding may be a common problem but

should a second opinion concerning the advisability of hysterectomy be given by a family practitioner? Some of them think so, but not all of us would agree.

The field of emergency medicine is developing rapidly. Legislation is appearing requiring that hospital emergency rooms have full-time physician staffing. This is laudable for the care of patients with true acute emergencies. However, many of the patients who present themselves to emergency rooms do not have acute emergencies but have simply chosen this avenue as the most practical way to see a physician. Who should care for those patients and who should determine the necessity for admission to the hospital or for transfer of the care of that patient to another physician? Many of us think we should make these decisions.

From within our specialty changes are occurring which might restrict the activities of our resident graduates in the future. The subspecialties have appeared—gynecologic oncology, maternal-fetal medicine, and reproductive endocrinology. Would it be possible for our specialty to be divided into many subgroups? Possible, but I think unlikely. Internal medicine has gone that route and now, based in part on deficiencies which have come to light, programs in general internal medicine are reappearing. We could learn from this experience. We have at least avoided the difficulty of creating independent boards and our subspecialists have received certificates of special competence with a continuing emphasis on the necessity of having competence in general obstetrics and gynecology before and after receiving the special certificate. Still there remains the significant concern that particular procedures may in the future, not be authorized for those not holding the special certificates and so there are concerns about the numbers of these certificates being awarded. In June, 1978, the written examination in gynecologic oncology was passed by 35 candidates; the examination in maternal and fetal medicine, by 76 candidates; and that in reproductive endocrinology, by 55 candidates. Past experience indicates that not all of these individuals will also pass the oral examination. For example, in 1977, the oral examination in gynecologic oncology was passed by 29 candidates; that in maternal-fetal medicine, by 37 candidates; and that in reproductive endocrinology, by 14 candidates. It seems likely that the numbers of candidates will not increase markedly in the near future.

Our specialists themselves have taken steps which reduce their spheres of activity. I refer to the relinquishing of certain tasks to midwives, nurse-practitioners, childbirth instructors, and other individuals. Originally much of this was done to combat the shortage of physicians but that shortage is rapidly disappearing. In 1953, there were approximately 135 active physicians per 100,000 persons in the United States. By 1985, there will be 200 and by the year 2000 there will be approximately 260 physicians per 100,000 individuals or one for every 385—and this estimate may be conservative.[6] Now, however, some of our specialists have become accustomed to delegating some tasks and they no longer see their patients with vaginal discharge, or the patients with questions about normal pregnancy, or the patients who come in for periodic examinations, or those with questions about sexual problems. At times one wonders about which patients they *do* see. One also wonders about the patients who complain of vaginal discharge but are worried about the possibility of cancer and would like to discuss it with their compassionate physicians.

So we see that our young graduates are pulled in both directions. The requirements of their certifying board and the realities of women turning to them with all of their medical (and sometimes other) problems require that our specialists remain well informed about general medicine—and well they should. The great majority of surgical specialties have a corresponding medical specialty and frequently the diagnostic aspects of the patient's management are carried out by the medical specialists while the surgical specialist confines his interest to the surgical treatment of the patient. Obstetricians and gynecologists, however, take the responsibility for both the medical and surgical aspects of their patient's problems.

On the other hand, the possibility exists that certain of the activities traditionally performed by obstetrician-gynecologists may be performed by others in the future, thus narrowing the sphere of activity within the specialty.

If one gave away the complicated problems to the subspecialist and the "simple" problems to the various physician extenders, the practice in our specialty would certainly be different from that which we have known and I question that it would be as interesting. Our society can do much to keep that from happening and I feel that it is uniquely qualified to do so.

I have stated that the Pacific Coast Obstetrical and Gynecological Society is different, and indeed it is. Our founding fathers had so much wisdom. They did not found an association, or an academy, or a section, but a "society." "Companionship or association with one's fellows; usually friendly or intimate intercourse; company" are Webster's definitions. "Society" is derived from the Latin *societas,* "meeting an associate." How appropriate that is for our organization. Our title is not as imaginative as some. Consider, for example, Ancient Mystic Order of Bagmen of Baghdad, Concentrated Order of Hoo Hoo, or Iridescent Order of the Iris. The latter is so impressive that it moved a journalist in

Springfield, Missouri, to write in 1914: "Just think of it. The Magnanimous Supreme Ruler of the Iridescent Order of the Iris was arrested in New York City the other day and thrown into a horrid jail! There must be something awfully wrong with the laws when such things can be done to a man with such a lovely title."

The Order of Pink Goats was organized in 1919. The members appeared in public in pink pajamas and gowns, carrying goats of all kinds and descriptions. The supreme officer was known as He Goat and some of the other titles were Little White Goat, Chief Bleater Goat, Chief Billy Goat, Chief Wise Goat, Goat Getter, Inner Angora Goat, Bell Goat, and Musical Goat.

I believe that my favorite is the Ancient and Honorable Order of the Blue Goose. It was founded in 1906 B.P. (i.e., before prohibition) mainly for "fun and sociability." What other organization can boast of Most Loyal Gander (president), Supervisor of the Flock (vice president) Custodian of the Goslings (warden) Wielder of the Goose Quill (secretary), and Keeper of the Golden Goose Egg (treasurer)?

But what is the nature of *our* society? Certainly it is viewed differently by different observers. Some would have us be a straight-forward scientific society with our programs limited to the presentation of scientific reports. There are many forums for such presentations and it is doubtful that there is a need for one more of the stereo-typed variety. Can the Pacific Coast Society offer anything different or of value greater than that of the multitude of scientific meetings and postgraduate courses? Yes, I think that it can, and I believe that the format of our meetings is a very important factor. Despite the attempts of many organizers to make it possible to discuss the presentations with the speakers it is rarely possible to pursue these discussions in sufficient detail because the formality of the meeting, or the size of the meeting, or the limited time prevents it.

How much better it is to be able to spend several days with the speakers and to have a number of informal opportunities to discuss their reports. This is one of the principal reasons for keeping our meetings from growing too large. Many organizations have started with a small group of truly interested members and during those early years discussion was productive and progress was great but now that the societies are larger the members reflect wistfully upon the early, stimulating days, or they look regretfully upon the formation of a new society of "Young Turks" who have become dissatisfied with the status quo. Our founders and early members have shown great wisdom in keeping the society small but also maintaining a steady flow of young, vigorous members into the group.

At so many medical meetings one sees the subspecialists presenting papers to their own group, discussing those papers with each other, and then returning home without having had much contact with members who do not share their particular interest. The result is that many of the physicians who manage all of the problems in the specialty begin to think that they are not qualified to understand the topics under discussion and gradually stop attending those sessions.

How much better is the atmosphere at the meetings of the Pacific Coast Obstetrical and Gynecological Society. It is not broken up into small groups and almost everyone in attendance hears all of the papers. If something is not clear or is controversial there is plenty of time for discussion and there is virtually endless opportunity for clarification—at the poker table, the golf course, or, yes, even the hospitality room.

Medical practice should be far from just work. I do not know of a group who goes about their daily activities with so much fervor and downright enjoyment as do physicians. But even we can be guilty of "all work and no play." Our society also helps with the maintenance of the balance between these two but lest any of you has not received that message I shall leave you with just one more quotation, whose author, unfortunately, is unknown.

If you hold your nose
To the grindstone rough
And hold it there
Long enough
In time there will be
No such thing
As brooks that babble
And birds that sing
Of these three things
Your world will compose
Just you, the stone
And your damned old nose.

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Endotoxin shock in the beagle dog

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The hemodynamic and metabolic responses to endotoxemia were assessed in seven splenectomized, chronically instrumented, conscious but lightly sedated beagle dogs. Measurements included: cardiac output (CO), right and left atrial pressures (RAP, LAP), systemic and pulmonary arterial pressures (SAP, PAP), and heart rate (HR). Arterial blood samples were measured for blood gas tensions, pH, lactate, and pyruvate. After a brief control period, 1 mg/kg endotoxin (Difco 026:B6) was given as an intravenous bolus. Two hours later, each animal was treated with low–molecular weight dextran (LMDX), 2 ml/kg/min for 15 minutes. Endotoxin initially produced a precipitate decline in CO, HR, RAP, LAP, and SAP with concurrent pulmonary hypertension; both pulmonary and systemic vascular resistance increased significantly, then declined to control values as the animal partially recovered. A progressive metabolic acidosis with excess lactate accumulation developed. LMDX produced a significant increase in CO, SAP, PAP, and LAP with a decrease in HR; RAP increased slightly. With hydration, hemodilution was noted along with relief of the metabolic acidosis and the oxygen debt. We conclude (1) neither pulmonary nor systemic vasconstriction persisted in the shocked dog, (2) the response of the pulmonary and systemic vascular beds to endotoxin was qualitatively similar, and (3) oncotic fluid therapy appeared to restore the hemodynamic and metabolic parameters to preshock values. (AM. J. OBSTET. GYNECOL. 134:120, 1979.)

A VERITABLE AVALANCHE of publications concerned with the basic pathophysiology and clinical management of shock, more specifically gram-negative endotoxin shock, has appeared over the past two decades. While much in experimental animal studies is of questionable relevance to human disease because of the artificiality of the experimental system (as well as species specificity), it is nonetheless pertinent to observe that provocative findings in the experimental animal do lead to appropriate research in humans.

Unfortunately, much of the artificiality referred to concerns the use of acutely instrumented mongrel animals, often of poor quality, anesthetized, artificially ventilated, sedated with various combinations of barbiturates and opiates, and often subjected to extensive major surgical procedures, heparinization, and other variables which influence the preparation significantly.

The present report deals with the preliminary results of an ongoing effort designed to reassess the typical hemodynamic and metabolic changes which follow the administration of *E. coli* lipopolysaccharide in a chroni-

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**Minority Biomedical Support Program Undergraduate Students.*

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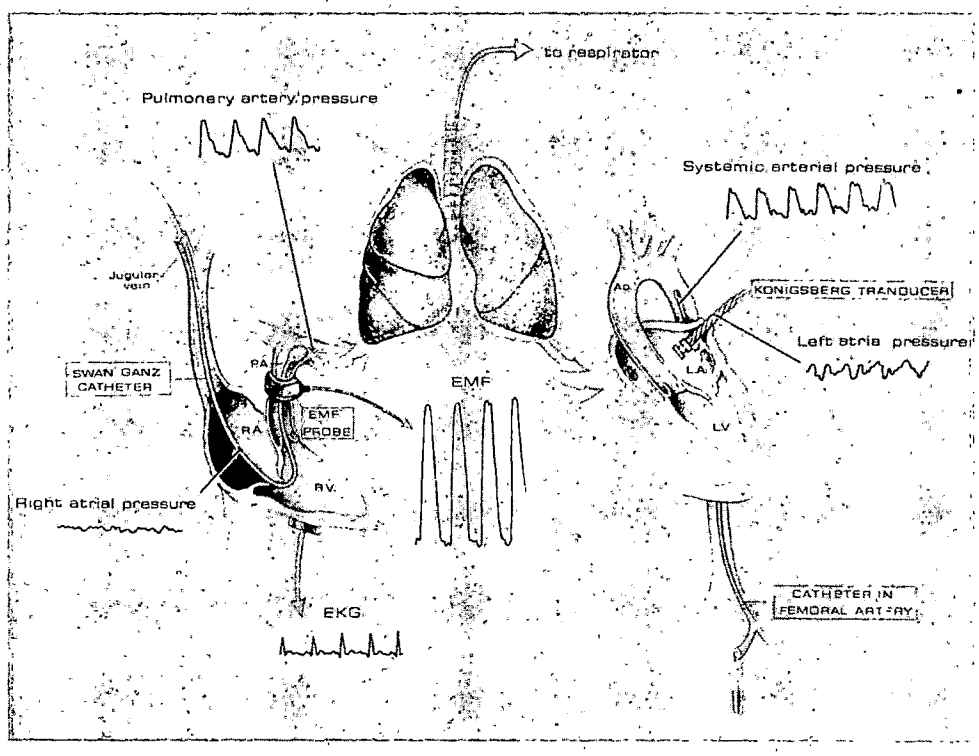


Fig. 1. Schematic illustration of surgical preparation (see text for details).

cally instrumented, conscious population of beagle dogs. The response of this population of control animals will be used to contrast the responses of a similar population of animals treated before and after shock with various vasoactive amines and humoral modifiers.

Material and methods

Beagle dogs of either sex, 6 to 7 months of age, and of uniform weight (average 8.0 kg) were obtained from a supplier* and evaluated carefully over the next 4 weeks in a certified experimental animal facility for anemia, parasitic infestations, intercurrent disease, or other processes which might interdict their use. Thereupon, each animal was prepared in two stages.

Stage 1 included a left lateral thoracotomy and pericardiotomy under general anesthesia (1.5% halothane and a 50/50 mixture of nitrous oxide and oxygen) utilizing a Bennet BA-4 respirator. The pulmonary artery (PA) was dissected free of the aortic arch and a precalibrated electromagnetic flow meter transducer† of appropriate size was placed about the PA to measure cardiac output. A precalibrated 3.5 mm outside diameter micropressure transducer‡ was secured in the left atrium to measure left atrial pressure. The chest wound was repaired after exteriorizing the silicone rubber–invested wire leads; these were buried subcutaneously. The spleen was then exposed through a midline incision in the upper abdomen, decompressed by the injection of 0.1 ml of a 1:1,000 epinephrine solution into the splenic artery, then removed. The animal was allowed to recover over the next 2 to 3 weeks.

In Stage 2 each dog was premedicated with morphine sulfate, 1 mg · kg^{-1} body weight. An endotracheal tube was inserted to ensure an adequate airway. The femoral artery was exposed under local anesthesia and cannulated with a polyvinyl catheter in order to measure systemic arterial pressure and to collect arterial blood samples. The electromagnetic flow meter and micropressure terminals were exposed and connected to a physiologic amplifier.*

A triple-lumen 7 Fr. Swan Ganz balloon catheter was floated down on the exposed jugular vein into the pulmonary artery. Location was assured by monitoring the characteristic pulsatile waveform. Pulmonary arterial pressure and pulmonary artery wedge pressure were obtained through the distal port. The proximal port, 20 cm from the distal port, lay within the right atrium

*Marshall Beagles for Research, North Rose, New York.
†Micron Industries, Los Angeles, California.
‡Konigsberg Industries, Pasadena, California.

*Electronics for Medicine VR-6, White Plains, New York.

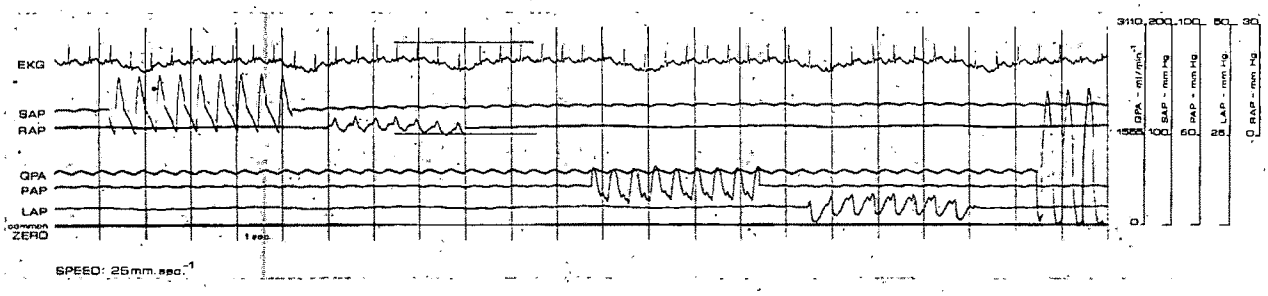


Fig. 2. Analogue signal display of six simultaneous hemodynamic parameters. Pulmonary artery flow *(QPA)*, SAP, PAP, and LAP, all have a common zero baseline; RAP zero centered 50 mm ↑. Scalar values on right-hand ordinate appear for each parameter. Phasic swings in electrocardiogram signal reflect respiratory rate. Pulsatile and electronically average signals are displayed.

and it was connected to another pressure transducer to measure the right atrial pressure. This pressure was considered the hydrodynamic equivalent of central venous pressure. The zero reference level for systemic arterial, pulmonary, and right atrial pressures was assumed to be the animal's midsternum as it lay in the lateral recumbent position. Finally, a standard limb Lead I electrocardiograph was attached. The complete preparation is illustrated in Fig. 1.

After a 30 minute control period, each animal was shocked with the intravenous bolus administration of 1 mg · kg^{-1} *E. coli* lipopolysaccharide (Difco 026:B6, lot 613872); the toxin was administered over a 15 second interval. A continuous recording of the changes in flow, pressure, heart rate, and electrocardiogram was made over the next 5 minutes. Another set of values were made at 15 and 30 minutes after the toxin had been administered and thereafter at 30 minute intervals for a total elapsed time of 2 hours. Thereupon, a 10% solution of low-molecular weight dextran (Rheomacrodex; LMDX-40) in saline was administered through a forelimb vein at a rate of 2 ml · kg^{-1} · min^{-1} over a 15 minute interval. Hemodynamic data were measured at the end of the infusion and again 45 minutes later. The animal was killed with a supersaturated solution of potassium chloride and the electromagnetic flow meter transducer and micropressure transducer were recovered; the relative position of the Swan Ganz catheter in the heart was ascertained.

Arterial blood samples were obtained during the control period, again at 1 and at 2 hours after administration of the toxin, and just prior to terminating the experiment. Blood gas tensions (O_2 and CO_2) and blood pH were measured*; hematocrit was also measured. Base excess was calculated from the Siggaard-Andersen nomogram. Arterial lactate and pyruvate were measured using standard kits* and excess lactate, a measure of oxygen debt, was calculated by the method of Huckabee.[1]

Both pulsatile and electronically averaged (mean) pressure and flow signals were displayed and allowed simultaneous measurement of systemic arterial pressure (SAP), right and left atrial pressures (RAP, LAP), pulmonary artery pressure (PAP), and, intermittently, pulmonary artery wedge pressure (PAWP), as well as heart rate (HR) and cardiac output. Total pulmonary vascular resistance (TPR) and total systemic resistance (TSR) were derived from standard formulas wherein resistance is the quotient of pressure (in millimeters of mercury) × 100 divided by flow (in ml · min^{-1}). Resistance was expressed as Green's[2] peripheral resistance units.

Results

Resolution of surgical and technical problems. Almost two thirds (19/33) of the dogs suffered major surgical and postoperative complications (hemorrhage, sepsis, wound disruption, and death). Much of this was the result of surgical inexperience and improper implantation of the atrial micropressure transducer as well as not allowing the animals sufficient time to recover from the earlier surgery. More recent experiments have been successful and we have complete data on seven dogs. Detailed statistical analysis is pending completion of an additional three animals.

Possibly the most troublesome biophysical signal was that obtained from the micropressure transducer in the left atrium. Zero baseline shift and drift were observed which were compensated for during the control period by using the PAWP as the reference standard to which the mean left atrial pressure was matched. No future adjustments in LAP signal were made thereafter as any

*Model IL, No. 213 digital pH blood gas analyzer, Lexington, Massachusetts.

*Sigma Chemical Co., St. Louis, Missouri.

discrepancies in the shock interval were considered physiologic and not artifactual.

Fig. 2 depicts the typical analogue signals obtained with the VR-6 physiologic recorder. All signals were calibrated from a common zero to a 100 mm full-scale deflection except for (1) the unquantified electrocardiogram display and (2) the RAP zero, which was arbitrarily placed in the center of the strip (i.e., 50 mm up from the common zero). Pulsatile and electronically averaged signals were displayed.

Changes in hemodynamics. The changes in both mean cardiac output (equal to pulmonary artery flow) and heart rate are illustrated in Fig. 3. The changes from control status, over the next 5 minutes following the injection of endotoxin and over the next 2 hours as well as the response to low–molecular weight dextran, are plotted. The profound fall in cardiac output was accompanied by a fleeting tachycardia whereupon the heart gradually decelerated (−20 bpm). The nadir of the response was invariably reached in the first 5 minutes. Thereafter the animal partially recovered so that 75 to 90 minutes later cardiac output had been partially restored to preshock levels and a significant tachycardia was evident; cardiac output then began to decline while HR remained elevated. A dramatic increase in cardiac output and a concomitant fall in HR characterized the response to the infused dextran.

Fig. 4 illustrates the changes in mean systemic and pulmonary pressure in this same group of seven dogs. Delta (Δ) SAP, the *net* pressure across the systemic vascular bed, was derived from the mathematical difference of SAP minus RAP. Since RAP is a relatively trivial value when compared to SAP, ΔSAP is not significantly different from mean SAP. The change in SAP was characteristic: A profound hypotension occurred initially, with little evidence of recovery, then a persistent hypotension developed which was corrected dramatically with the dextran. In contrast dextran barely increased RAP (<6 mm Hg); mean atrial pressure was still well within the physiologic range.

ΔPAP, the net pressure across the pulmonary vascular bed, equal to mean PAP minus LAP, is similarly depicted in Fig. 4. Pulmonary hypertension developed immediately after the injection of endotoxin and was associated with a significant fall in LAP. The changes persisted for another 45 to 60 minutes, then returned toward preshock values. The dextran initially produced a sharp increase in PAP and LAP but the former was not persistent, returning to preinfusion levels.

A comparison of the changes in systemic and pulmonary vascular resistances is depicted in Fig. 5. The resistance calculations assume that left ventricular output is

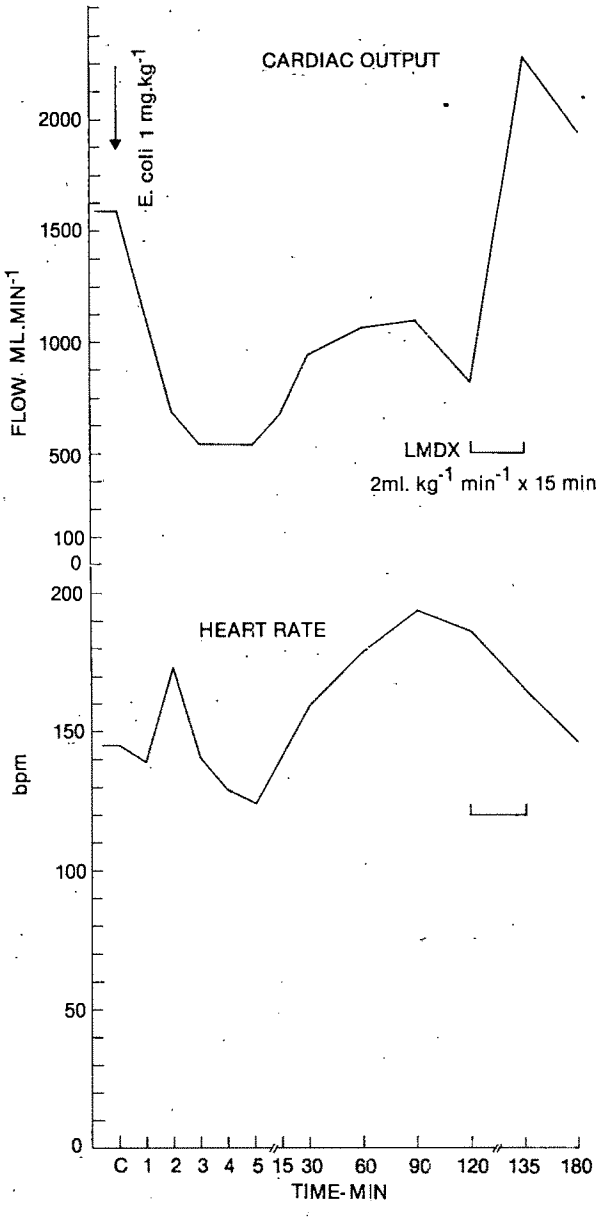


Fig. 3. Effect of intravenous endotoxin on mean cardiac output and heart rate in seven dogs, emphasizing acute dchanges over first 5 minutes and over 2 hours and the response of the shocked animal to low–molecular weight dextran.

equal to the measured right ventricular output, and thus that fraction of left ventricular output which feeds the coronary arteries (and which may be relatively substantial in the shocked animals) is not taken into account. Thus, TSR is inherently underestimated. Nonetheless, the significantly lower control values in the pulmonary bed as compared to the systemic vascular bed are consistent. At first glance, it is evident that both vascular beds appeared to behave in a similar manner, with the peak TPR being slightly (1 minute) later than

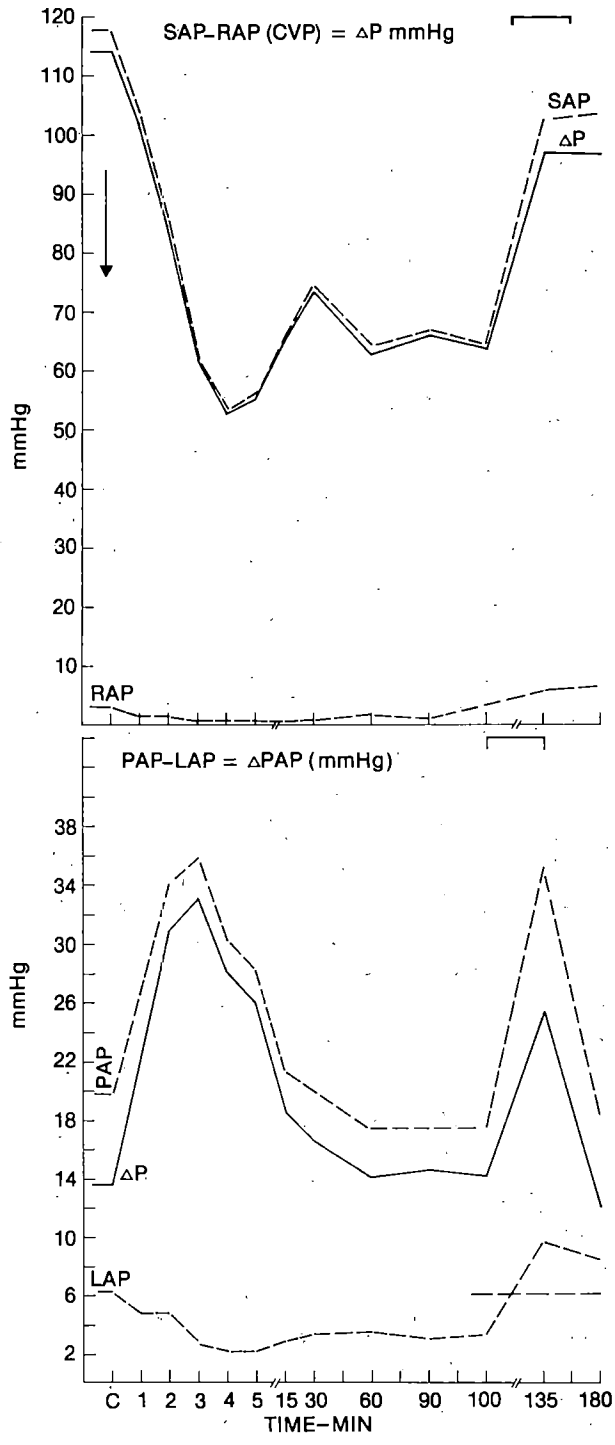


Fig. 4. Effect of intravenous endotoxin on mean SAP, RAP and ΔP (SAP − RAP) as well as pulmonary vascular equivalents (PAP, LAP, and ΔP = PAP-LAP) in seven dogs. Whereas RAP shows little increase with LMDX, note significant change in PAP, LAP, and ΔP.

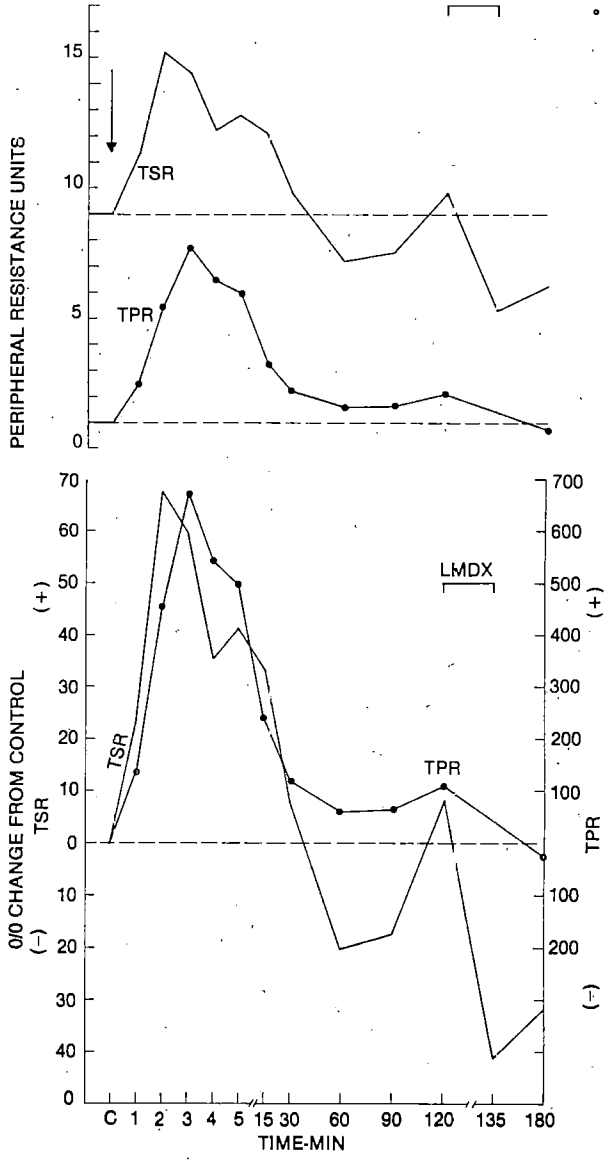


Fig. 5. Effect of intravenous endotoxin on mean TSR and TPR in seven dogs as well as response of shocked dogs to LMDX. Data are also plotted as percent change from control; note tenfold difference in scalar ordinates.

the peak TSR. Both resistances returned to control values about 60 minutes later, with the TSR falling below control levels during the relapsing phase. The response to the volume overload was striking and consistent in each animal: a significant fall in TSR with little change in TPR. The extent to which this fall in TSR reflects an alteration in blood viscosity and rheology rather than an inhibition of peripheral sympathetic activity in response to baroreceptor stimulation[3] is speculative. Nonetheless, the dissimilarity in the two vascular beds is noteworthy.

While a comparison of the changes in vascular resis-

Table I. Changes in arterial blood pH, blood gases (oxygen and carbon dioxide), hematocrit (Hct), base excess (BE), and selected metabolic parameters (arterial lactate, pyruvate, and computed excess lactate) in the shocked dog and after volume therapy

Parameter	*Control*	*S + 60*	*S + 120*	*D + 60*
pHa (units)	7.35	7.30	7.33	7.34
Pao_2 (torr)	109	75	98	82
$Paco_2$ (torr)	51	42	36	45
Hct (vol %)	38	42	41	27
BE (mEq/L)	+1.4	−5.5	−6.3	−1.4
Arterial lactate (mg/100 ml)	11.2	25.1	27.7	19.3
Arterial pyruvate (mg/100 ml)	1.04	1.76	1.43	1.54
Excess lactate (mg/100 ml)	—	6.70	10.3	2.62

S + 60 and S + 120 denote time in minutes after 1 mg · kg^{-1} of an intravenous bolus of *E. coli* lipopolysaccharide and D + 60 is the time in minutes after administration of LMDX−40, 2 ml · kg^{-1} · min^{-1} x 15 minutes.

tance does suggest a qualitative similarity, the true assessment of the *quantitative* disparity is reflected by expressing the resistance changes as a percentage of control. Percent changes in TSR are shown (in Fig. 5) in the left-hand ordinate and those for TPR are in the right-hand ordinate. The scalar changes in TPR are tenfold those of the TSR. The increased sensitivity of the pulmonary vascular bed to endotoxin when compared to the systemic vascular bed is re-emphasized. Exactly how different components of the systemic vascular bed (i.e., liver, kidneys, gut, and muscle) behave cannot be derived from this experiment.

Metabolic changes. The metabolic indices and response to shock and to volume therapy are summarized in Table I. The occurrence of a progressive metabolic acidosis and of lactate accumulation, reflecting an increasing oxygen debt, is demonstrated. The hemodilution secondary to volume therapy may have contributed to the *apparent* reduction in metabolic acidosis and oxygen debt but also may well reflect improved tissue perfusion, oxygenation, and aerobic metabolism.

Comment

This study, still in progress, was designed to establish a uniform experimental animal model for the study of endotoxic shock in which the usual variables of acute surgery, i.e., anesthesia, ventilatory support, vasoactive drug (barbiturates), heparinization to maintain catheter patency, uncontrolled blood sampling, and the like, are minimized. That objective appears to have been accomplished so that our next goal—to determine what role the prostaglandins play in the pathophysiology of endotoxic shock—can be approached. Recent studies suggest that the genesis of pulmonary hypertension in septic shock in the dog,[4-6] cat,[7] and sheep[8] is mediated by the prostaglandins.

While it would have been tempting to use, as a control population, the findings reported[9, 10] several years ago by one of us (J. A. M.) in an acutely instrumented, anesthetized, and artificially ventilated population of mongrel dogs with intact spleens, we elected instead to revalidate that report with the present model. Surprisingly, perhaps, the current findings are comparable except in two regards. First, pulmonary hypertension and pulmonary vascular resistance appeared to be persistent and biphasic in the mongrel dog. While both parameters increased in a similar manner immediately after the administration of endotoxin in both groups of dogs, PAP and PVR were reported[9, 10] to be sustained in the mongrel dog and did, in fact, appear to increase again as the animal relapsed. No such persistent or biphasic effect has been noted in the beagle dog. The genesis of the pulmonary changes is still speculative and has been attributed to a variety of stimuli, i.e. (1) a reflex neurogenic vasoconstrictor response to microembolization (platelet aggregation?) and (2) the release of humoral vasoactive substances (histamine, serotonin, prostaglandins). Whatever the stimulating factor(s), the present studies do not suggest that the alterations in the pulmonary and systemic vascular beds are dissimilar except in a quantitative manner with the former seemingly more intense.

Second, whereas hemoconcentration developed in the mongrel after shock, such was not the case in the beagle. Earlier it was thought that the hemoconcentration developed as plasma leaked across damaged endothelium.[10] The data in the splenectomized beagle do not support that premise, at least not during the 2 hour shock interval. Most likely, the postshock increase in hematocrit observed previously was due to splenic contraction whereby 8 ml · kg^{-1} · body weight of red blood cells may be added to the circulation.

The genesis of the acute reduction in cardiac output, heart rate, and SAP along with a marked increase in pulmonary and systemic vascular resistance is unknown. Seemingly, a large volume of blood is trapped peripheral to the heart in either the pulmonary vascular tree (increased central blood volume) and/or the

peripheral microcirculation. A "tourniquet" effect has been postulated in which postcapillary sphincter (venular) spasm predominates. In turn, venous return to the heart falls. Presumably this is due, at least in part, to a massive sympathetic outflow with intense sympathoadrenal hyperactivity. If so, the effect appears to be transient and the hemodynamic changes are not modified by pretreatment with alpha-adrenergic receptor antagonism (dibenzyline).[9] Increased vagal activity may well explain the transient bradycardia since the usual physiologic response to acute hypotension is a reflex tachycardia. Finally, alterations in vessel compliance (distensibility) of the systemic vascular bed, particularly the capacitance vessels (the large veins), may well account for much of the "missing" volume.

The hemodynamic response to volume therapy is as expected and clearly illustrates the pathologic problem: impaired tissue perfusion secondary to the sequestration of blood volume peripheral to the heart.

Earlier it was thought that the hepatosplanchnic circulation was particularly sensitive in the dog to endotoxemia so that massive entrapment of blood in the gut and liver resulted from hepatic venovasoconstriction. A recent report by Guntheroth and Kawabori[11] raises serious doubts about that view. Further, myocardial dysfunction might impair cardiac output. However, the prompt response to osmotically active volume therapy confirms an earlier observation[12] that the pump appears intact and, if provided with volume, can distribute that volume without the need for supplementary cardiotonic or inotropic amine drugs. Further, with the increase in circulatory volume achieved with dextran, hemodynamic normalcy was restored along with an improvement in the metabolic indices. Those data stand in sharp contrast to an earlier finding[9] in which the hemodynamic parameters were restored with a vasoactive amine drug (metaraminol) but the metabolic indices deteriorated even further. Thus, treatment of the animal in shock with agents other than ones producing volume expansion will have to achieve results at least equal to those observed with oncotic fluid therapy.

Finally, the changes in right atrial (central venous) pressure in the shocked animal which follow volume therapy confirm other reports[13] which seriously question the validity of that parameter as an index of volume sufficiency. On the other hand, PAWP more accurately assessed cardiac filling and output.

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Do endorphin residues of beta lipotropin in hormone reinforce reproductive functions?

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The beta-endorphin residue of pituitary beta-lipotropin hormone, which regulates utilization and storage of body fat, is several times more potent than morphine in raising pain tolerance. It also produces habituation and dependency behavior. Recently it was found to be present in amniotic fluid and to be a releaser of prolactin. It now appears that the placenta is a rich source of endorphins. These findings may open a new chapter in understanding molecular determinants of behavior patterns responsible for natural selection and survival of vertebrate species. Clinical application of basic information and new concepts relating endorphins to maternal behavior patterns and neonatal physiology is the purpose of this communication. A brief review of the literature, some data from [^{3}H]opiate-binding assays, observation of maternal performance, and reports of maternity patients' feelings and motivations suggesting that these hormone molecules mediate formation of affectional attitude, appetitive systems, and maternal behavior will be presented. (AM. J. OBSTET. GYNECOL. 134:127, 1979.)

If we ask Nature the right questions and listen to what Nature is trying to tell us—she will give us the right answers.

Louis Pasteur

MANY REPORTS have now established the fact that 61 tyrosine fragments of the 91 amino acid sequence constituting beta-lipotropin hormone (BLPH), known as enkephalin ($BLPH_{61-65}$) and β-endorphin ($BLPH_{61-91}$), are considerably more potent than morphine in increasing tolerance to pain[13, 29, 31, 31a] and will produce addiction and dependency behavior patterns in vertebrate creatures.[32, 33]

Other reports have reliably demonstrated that these ubiquitous opioid molecules (1) are evoked by physiologic stress in parallel with adrenocorticotropin (ACTH),[9] (2) stimulate release of prolactin hormone necessary for production of milk,[8, 19, 34] and (3) suppress hostility, irritability, and anxiety and induce affectional grooming behavior as will small doses of morphine.[7, 30, 35] All of these reactions are completely reversed by the opiate antagonist naloxone which will displace both endorphins and opium compounds at nerve cell receptor sites.

The discovery of enkephalin was first reported in December, 1975.[13] Subsequent reports during 1976 lead to interesting questions: What purpose in biologic evolution and selective survival is served by a natural hormone that produces lactation, affectional behavior, and addictive dependency? Is it possibly related to physiologic mother-neonate interdependency? Contemplation of these teleological questions prompted our efforts to investigate beta-endorphin molecules in reproductive behavior.

It seemed logical that the placenta, which is well known as a steroid and peptide hormone "factory,"[4, 5, 24] should also produce β-endorphin under the physiological challenge of labor. In January, 1977, we began trying to acquire (from The Salk Institute in La Jolla, California) information regarding radioimmunoassay reagents to measure β-endorphin in amniotic fluid and blood plasma of mothers and newborn. Subsequently, in September, 1977, we were greatly pleased and stimulated when Dr. Roger Guillemin of The Salk Institute with Dr. J. P. Gautray and his colleagues of Creteil, France, reported that β-endorphin, as we had anticipated, is evoked in amniotic fluid during labor.[6] It rises as much as twentyfold during difficult and prolonged labor and thus is an indicator of fetal distress. They also found that lowest assays in amnitoic fluid from cesarean births and considered the infant pituitary to be the source of beta endorphin.

Early in 1977, we began storing frozen amnitoic fluid

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and plasma from umbilical cord and maternal blood. The samples were from unmedicated mothers during labor and shortly after birth. Most mothers who actively participate in normal physiologic labor tend to manifest high emotional elation and euphoria. We also collected frozen plasma samples of maternal blood before and soon after periods of breast-feeding to test for circulating endorphins. Small samples of colostrum and meconium were also collected and stored to be tested for the possible presence of endorphin-releasing enzymes.

Mothers (and a few participating fathers from whom plasma samples for endorphin assay were also collected) were graded on a maternal aptitude and performance scale similar to the Apgar score. Their subjective feelings and emotional attitudes were elicited at intervals during the first postpartum trimester. Most, but not all, of this small group of expectant parents had attended prenatal classes oriented to active participation in childbirth and breast-feeding.

In December, 1977, Dr. Henry Yamamura generously offered to assay the opioid molecules in our samples at his laboratory at the University of Arizona.

Methods

The[^{3}H]naloxone-binding assay[27, 28] is a sensitive and convenient method to measure opium receptor ligands in biologic fluids. Specific radioimmunoassay to identify human beta lipotropin[18] and alpha and beta endorphin[11, 25] were recently reported but antibody sera and labeled antigens are not yet available to us.[10, 10a] Enkephalin radioimmunoassay reagents are commercially available but rapid tissue enzyme degradation and the brief half life of the pentapeptides negate their use in this clinical study.

Observations of physiologic performance and behavior of mothers and infants were made. Maternal mood reactions and emotional impressions were elicited by semistructured interviews to be correlated later with endorphin assays.

Results

N. E. Pedigo and H. I. Yamamura have graciously made it possible for me to be the first to report that the placenta appears to be a rich source of natural endorphin opiates. Using [^{3}-H]naloxone binding they found that homogenized extracts of placenta from normal, unmedicated, term births will yield approximately 200 μg (60 nmoles) of opioid substance per gram of tissue. This material is assumed to be β-endorphin which is the most stable of the BLPH opioid residues.

Assays of our frozen plasma and amniotic fluid samples are in process. Results were not yet available at the time of this writing.

Comment

In the light of evidence available at present, several statements can be made with reasonable validity. Molecules that bind opioid receptors are generated by the placenta during physiologic labor. Physiologic stress and insulin-induced hypoglycemia elevate circulating BLPH,[18] ACTH,[9, 24] melanocyte-stimulating hormone,[4] prolactin,[33, 34] and endorphin opiates.[9] Presence or absence of endorphin opiates influences moods and feelings. Feelings modulate perception and thinking. Thinking controls behavior. To quote Barchas and colleagues,[2] of the Department of Psychiatry at Stanford, "There is compelling evidence that behavioral events alter neurochemical functions and that altered neurochemical functions can change behavior." β-Endorphin increases in amniotic fluid as much as twentyfold during parturition and may reflect fetal distress in prolonged and difficult labor.[6]

Opiates stimulate prolactin[8] and breast milk secretion, which motivate feeding and nurturing behavior.[5, 35] Prolactin is suppressed by naloxone.[34] Opiates also reduce hostility, irritability, and anxiety and induce affectional grooming behavior which naloxone reverses.[7, 35]

Perineal analgesia is usually present in the second and third stages of normal physiologic labor. The euphoria and high elation manifested by most women following physiologic birth of their infants are quite comparable to those evidenced by narcotics addicts following intravenous injection.[30, 35] Mothers experienced in breast-feeding report enjoyable mood and affectional feelings during nursing which some state are similar to their reactions to codeine and Percodan. The fact that affectional behavior is induced by endorphin and prolactin, both of which are antagonized by naloxone, implicates this combination of peptide hormones in the structural-functional modality[1, 12] of care-giving behavior, the mother-infant pair bond, and other affectional relationships.

This raises another question: Does our North American custom of promptly cutting the umbilical cord and removing the placenta following birth deprive mothers and infants of placental opioid molecules designed to induce interdependency of mothers and infants? Failure of this structural-functional hormone physiology at such a critical time in mother-newborn neural programming experience may result in reward frustration. It may also set autonomic patterns for paradoxical maternal apathy or antipathy observed experimentally in subhuman species[26] and in battering mothers who were deprived of normal neonatal imprinting experi-

ence.[15, 15a, 16] Inability to generate and respond to endorphin and prolactin may be the mechanism responsible for autistic intolerance to physical intimacy, psychosexual dysphoria, self-destructive depression, drug addiction, and the sociopathic alienation of disaffected youth, which has increased during the past two or three decades.[35] β-endorphin injections produce a remedial influence on mood and behavior of mental patients.[14, 17]

Recent reports indicate ACTH and prolactin will prevent onset of respiratory distress syndrome (RDS) and fatal hyaline membrane disease in premature infants born wih low lecithin/sphingomyelin ratios and with plasma prolactin levels below 200 ng/ml. Morrison[21, 22] in a double-blind study of 126 premature births stated that administration of 500 mg of hydrocortisone to mothers early in premature labor results in a significant decrease in RDS and infant mortality rates. Mendelson[20] reported that RDS did not occur in neonates with cord blood prolactin levels above 200 ng/ml but was present in 80% of 191 premature infants with cord blood prolactin levels below 200 ng/ml. Mendelson also pointed out that opiates stimulate prolactin and that RDS is extremely rare in premature infants born to heroin-addicted mothers. She suggested that prolactin is the natural trigger for surfactant synthesis in the fetal lung. It appears more probable to us, however, that the ACTH and β-endorphin molecules generated by the term placenta during active labor are responsible for elevation of fetal corticosterone, prolactin, and lung surfactants and act to prevent onset of RDS and hyaline membrane disease.

Returning to the question posed in the title of this paper, it is central dogma in biology that evolution and survival depend on nature's system of selecting the fittest to survive and propagate. It is a basic tenet of psychology that extinction of a behavioral pattern occurs if the reinforcing rewards fail to be provided. It is a matter of common agreement that sexual intercourse is a powerful reinforcer of affectional behavior and propagation and that opiates induce compulsive behavior and addiction. Given the fact that physiologic labor has been shown to generate significant amounts of placental opioids, it appears that placental endorphin is nature's payoff for physical stress and hard labors connected with making, bearing, and feeding new members of each oncoming generation. Thus, endorphins provide the emotional reward to reinforce biological behavior that contributes to propagation of the species and advances cultural evolution.[15, 16] This means to say that mothers normally enjoy conceiving, birthing, and feeding babies and normal fathers enjoy doing these with them.

We now postulate that endorphin molecules provide the physiologic rewards to reinforce maternal affect and compel nurturing behavior as well as motivate paternal dominance and protection of dependents in the family unit. In other words, it appears that biologic events beginning at puberty such as courtship, mating, birthing and feeding of young, and defense of dependents and territory will generate BLPH residues and create appetitive needs to repeat activities which supply endorphin ligands to satisfy natural opiate receptors. Placental endorphins generated during labor reward the mother's birthing effort, arouse her appetite for opiate receptor ligands, stimulate prolactin, and initiate feeding-nurturing behavior.

Deprivation and failure to achieve satisfaction of innate biologic appetites, which include endorphin rewards and sexual gratification, result in frustration and the development of compensatory substitutes, some of which may be sociopathic or self-destructive. For example, lacking the endorphin feedback that normally accompanies physiologic birth and stimulates lactation, some mothers tend to become depressed with postpartum "blues" or annoyed and irritated instead of rewarded while serving their infants' continuing and insatiable demands for food and attention. This frustration of affectional communications leads to more or less autistic behavior, the extreme examples of which are the asocial motherless monkeys, reported by Seay and colleagues,[26] that abused, rejected, and battered their firstborn infants. Other examples of compensatory mechanisms might include excessive eating, proneness to drug addiction, angry, rebellious countercultural behavior, or mental illness.[3, 17] The fact that β-endorphin injections are reported by Kline and associates[17] to be a spectacular remedy for profound depression and long-standing schizophrenia suggests that recurrent endorphin depletion or inability to generate proper endogenous opiate receptor ligands may be of etiologic significance.

Our hypothesis that endorphins act as multifaceted biologic behavior regulators doubtless upset many deeply entrenched ideas of human behavior theory and engender vigorous or even violent opposition, as, for example, the Wilson-Lewontin[36] controversy over sociobiology. Despite the tendency to cling to long-cherished beliefs, the truth will eventually prevail. Micromeasurement of these neuroregulators of survival behavior mechanisms is now possible and sooner or later will provide a factual molecular foundation for a structural-functional science of behavior.

The growing trend toward the age-old "do it yourself" method of physiologic birth and infant feeding advocated by the Childbirth Education Association and

LaLeche League reflects the innate wisdom of women in matters of reproductive biology and family survival. Newborn infant brain circuits require specific affectional input to program neurohypophyseal production of endorphin hormones necessary for basic security and independent identity.

To conclude that opioid residues of beta-lipotropin hormone do not exert significant and compelling influence on reproductive and survival functions would deny the self-evident logic propounded in Darwin's *Origin of the Species* and Teilhard deChardin's *Phenomenon of Man*[23] as well as the integrated evidence from molecular biology and behavioral science.

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Discussion

DR. EUGENE C. SANDBERG, Stanford, California: What I heard in Dr. Kimball's presentation is that he has initiated a project (which he hopes to complete) and he is excited about the anticipated results. He justifies both his enthusiasm and his pursuit of the project by citing results from recent research. Additionally, he speculates on the potential that continued research in the subject area discussed will provide an understanding of the basic neurochemical mechanism responsible for reproductive behavior. In formulating his thesis he has taken liberties with reported observations and conclusions, has exaggerated the profundity of certain findings, has made a number of unwarranted assumptions, and has offered what appear to be a number of extravagant speculations. It might be superficially justifiable and ephemerally entertaining to question, contest, or attack these areas of vulnerability. Such an approach, however, would serve only to generate a nonproductive tempest and would ignore the virtues of the presentation and the importance of the basic message which, oddly enough, at least as I perceive it, is not to be found in the presentation. Rather than chase the decoys (the endorphins and the enkephalins), I would like to offer my interpretation of the basis of and the motivation for Dr. Kimball's presentation and point out what I feel to be his important, but regularly neglected, contribution to the advancement of obstetric care. Some background information, undoubtedly presupposed as evident by Dr. Kimball because he has thought it and said it so frequently and for so long, provides the missing links that place today's presentation in perspective.

Broadly defined, ethology is the study of animal behavior. One aspect of ethology deals with the biologic forces that control reproductive behavior. This aspect includes maternal behavior toward the offspring that accentuates the potential for successful reproductive behavior by the offspring in turn, thus enhancing the prospects for perpetuation of the species. Dr. Kimball is devoted to this aspect of ethology and twice before, in 1966[1] and 1974,[2] presented to our Society eclectic data from this discipline. At one time, the concept prevailed that all reproductive behavior was genetically preprogrammed, instinctive, and not substantially modified by environment or experience. In his presentation in 1966, Dr. Kimball reviewed results of research demonstrating the importance of "imprinting" on the newborn animal's subsequent behavior, including that related to reproduction. Receipt by the infant of affection, security, warmth, protection, and fulfillment of needs by the mother (i.e., what most of us would term "appropriate maternal nurturing") was vital in establishing reproductively effective behavior in the offspring. For example, newly hatched goslings, "imprinted" by a human acting in the maternal role, followed and responded to the surrogate mother as other goslings did their natural mothers. The birds subsequently courted the human and failed to mate with their own kind. In other experiments, monkeys deprived of all maternal contact following birth subsequently could not form appropriate or typical relationships with other monkeys and failed or refused to mate. When reproduction was forced upon them by artificial insemination, an experiment suggested to the researcher by Dr. Kimball, the "motherless monkeys" totally ignored their infants from birth and rejected and even severely abused them when the infants sought maternal closeness. Many survived only through intervention by the investigator. In essence, behavior necessary for perpetuation of the species failed to develop in mother nurture–deprived animals, at least with the initial pregnancy. In humans, sociopathic behavior and emotional disturbances of various types, as well as subsequent abusive treatment of their own young, have been commonly noted in individuals deprived of effective maternal nurturing. A dozen years ago, Dr. Kimball asked the members of this society and fellow obstetricians everywhere to recognize these findings, to appraise the attitude and character of their obstetric patients, and to attempt to anticipate instances of lack of appropriate maternal nurturing in the hope that this requirement could somehow be afforded to the newborn infant by natural or surrogate means. This represented one of the earliest appeals to clinicians to bring the fruits of ethological research to clinical practice and to initiate preventive measures against the development of behavioral problems and emotional illness.

In his presentation 4 years ago, Dr. Kimball expanded on these points and added infantile autism and childhood depression and schizophrenia to the list of conditions inducible by the lack of maternal nurture. Most importantly, Dr. Kimball described his own practical attempt to prevent behavioral illness. He described the establishment of a program in Seattle in which inexperienced, inept, frightened, and potentially dysadaptive parents could be informed of the necessity for maternal nurturing and given adequate information and support to effectively provide this to their offspring. Because of the avant garde nature of the program and its tremendous potential, it would be interesting and important to learn of its results. Unfortunately, these have not yet been made available.

It is apparent that Dr. Kimball is desperately desirous of finding a molecular foundation and a "hard science" explanation for the "soft science" observations described to date in ethology and the other behavioral disciplines. In 1974, he looked hopefully to the experimentally popular neurotransmitters, dopamine and norepinephrine, for that foundation. In today's presentation, he looks hopefully to the hottest new items in neurochemical research, the endorphins and the enkephalins, for that support. Despite the certainty of their importance, most of which is yet to be determined, it seems unlikely to me that the endogenous opioids are as vital and basic to behavior and its evolutionary transmission as Dr. Kimball dreams them to be.

Regardless, I am grateful to him for drawing our attention to the opioids and for stimulating our minds with his enthusiasm. And while he pursues his laboratory research, I am hopeful that he will not forego his crusade to inform clinicians of the essentiality of maternal nurturing. I am hopeful that obstetricians will soon recognize an additional responsibility to the infant beyond the simple provision of a safe delivery. I am additionally hopeful that obstetricians will soon seek out pediatricians, child psychiatrists, psychologists, social workers, and others sensing a similar responsibility and establish programs in parenting and preventive psychiatry. Programs such as that outlined previously by Dr. Kimball and that recently described so eloquently in the Jacobi Lecture by Kempe,[3] a pediatrician working in the area of child abuse, are excellent examples. And last, as these things come to pass, and I feel they will, I hope that Dr. Kimball's efforts and foresight will not go unrecognized, unappreciated, and unrewarded.

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DR. JAMES C. CAILLOUETTE, Pasadena, California. I would feel remiss if I did not congratulate Dr. Kimball on this significant contribution. He has made persistent and repeated efforts to educate this society, and our specialty, on that most important subject, "behavior." In 1966, he introduced the word "ethology" to this group with his paper entitled, "Ethology in clinical obstetrics." I reintroduced the subject to this group in 1969 with my paper, "Ethology in the teaching of obstetrics and gynecology." Reassuring for Dr. Kimball, and for me, was the fact that in 1973 that most cherished scientific award, the Nobel Prize, was awarded to three ethologists: Konrad Lorenz, Nikolaas Tinbergen, and Karl von Frisch.

Until recently, nonverbal communication between members of the same species and members of different species was not understood and therefore skepticism persisted.

Today, in my opinion, Dr. Kimball has helped to break the code. He has told us about beta-endorphin residues and their effect on behavior—as well as their being a possible signal of fetal distress. Incidentally, I believe it is one of the current theories of the mechanism of acupuncture.

I would like to support Dr. Kimball's good work by adding yet another dimension to the subject of behavior. Another new word is "pheromone"—defined as "a substance, secreted to the outside of the body and perceived (as by smell) by another individual of the same or different species, releasing a specific reaction to behavior in the percipient."

In my opinion, the understanding of, and the ability to prudently control, behavior is what civilization is all about.

DR. KIMBALL (Closing). I was disappointed that no attention was paid to RDS, which I think at the moment is the most important aspect of our investigation of these molecules in maternal and cord blood which we think evoke prolactin. The future will, of course, tell the story. The circumstantial evidence is compelling. The factual data will be forthcoming. In regards to Dr. Sandberg's doubts regarding qualifications of this investigation, I am just really getting started at it. I hope to live long enough to see it culminated in some degree. I do think that within the next year or so we can determine whether, in fact, endorphin is the releaser for prolactin. Indeed, these molecules may be the mediator of a great many so-called survival behavior patterns—not only in our species but in the mothers of all other species which require reinforcing. Animals will not do anything without a reward, a payoff. When Dr. C. H. Li of the University of California at Berkeley began studying endorphins, he investigated the beta-lipotropin molecule in camels, because camels will go out and walk around the desert for days and their reward seems to be just going out and walking around on the desert. This suggested there must be something making them feel good about it—like joggers feel so good when they jog and some joggers get really high on jogging. It has been established and definitely established that acupuncture and the so-called transcutaneous electrical stimulator does increase endorphin in spinal fluid and will relieve intractable pain of cancer much better than morphine. This has been done at the University of California, San Francisco, in the Department of Neurosurgery. There is no question about the fact that an opioid molecule exists. We believe we have found it in the placenta, in relatively large amounts. We will see how it turns out.

Severe dysplasia and carcinoma in situ of the vagina

JOSEPH A. OLIVER, JR., M.D.
Pasadena, California

Papanicolaou smears for early detection of carcinoma in situ of the cervix has been a well-recognized method of screening patients for over 30 years. The necessity for Papanicolaou smears following hysterectomy, especially for benign disease, has been a controversial subject. Twenty-two cases of carcinoma in situ of the vagina, over a period of 18 years, at the Huntington Memorial Hospital in Pasadena, California, are presented. Ninety-five percent of the lesions were first suspected by use of the Papanicolaou smears. Approximately half of previous hysterectomies were performed for benign disease. The various methods of treatment employed and the complications in these patients are discussed. (AM. J. OBSTET. GYNECOL. 134:133, 1979.)

FOLLOWING HYSTERECTOMY, whether vaginal or abdominal, in situ carcinoma of the vagina is rarely seen, yet when it exists it must be diagnosed. Twenty-two cases were seen from 1960 through 1977. Abnormal Papanicolaou smears led to early detection of this disease. Treatment varied widely, and the methods of treatment, results, complications, and follow-up will be discussed. The use of iodine stain to localize the lesion and colposcopy in determining the extent of the disease prior to excision has been very helpful.

Because of the great similarity in abnormal vaginal and cervical cells, Papanicolaou smear for early detection of intraepithelial neoplasia of the vagina is a valuable method of detection of intraepithelial disease of the vagina.[1]

Carcinoma in situ of the vagina was first described in the American literature in 1952 by Graham and Meigs.[2] Moran and Robinson[3] reported a case in the Spanish literature in 1948. A malignant lesion of the vagina was first described by Cruveilhier in 1827. Early vaginal lesions by gross examination were recognized and reported by Mackenrodt[4] in 1896. Merrill and Bender[5] and others have pointed out the similarity between the natural history of dysplasia and carcinoma in situ of the cervix and vagina. In the 1940s and 1950s Hummer and associates[1] reported from the Mayo Clinic a series of unexpected abnormal Papanicolaou smears in a group of patients who, months or years earlier, had undergone hysterectomy for carcinoma in situ of the cervix. The prognosis in the intraepithelial stage is generally good, similar to that of carcinoma of the cervix, as pointed out by Hummer and associates[1] and Rutledge and colleagues.[6]

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Material and methods

Twenty patients with a diagnosis of carcinoma in situ of the vagina from 1960 through 1977 and two patients with severe dysplasia of the vagina were included in this series. Patients with invasive carcinoma of the cervix and vulva were excluded. There were no patients exposed to diethylstilbestrol in utero.

Results of treatment

Twenty-one of 22 cases were squamous in origin. One lesion was described as adenocarcinoma in situ, which occurred 7 years after total abdominal hysterectomy and bilateral salpingo-oophorectomy for adenomatous hyperplasia. These patients have been followed up for 6 months to 18 years. Twenty-one of 22 patients are still alive. Twenty of 22 patients are free of disease. One patient developed recurrent squamous cell carcinoma 4 years after vaginectomy and is alive with disease following pelvic radiation.

Twenty-one of 22 cases (or 95%) were suspected as the result of abnormal Papanicolaou smears obtained on routine pelvic examinations. Iodine stain was utilized in 17 of the patients and a nonstaining area with positive lesions was found in 16 patients (94%). Fourteen patients (64%) had a solitary lesion of the upper vagina. Eight patients (36%) had multifocal lesion involving primarily the upper vagina; in three patients the lesion involved the upper and lower vagina. Nineteen patients had undergone previous hysterectomy, 11 for benign disease and eight for carcinoma in situ of the cervix. Three patients had negative cone biopsy

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following abnormal Papanicolaou smears. Two of the three lesions were severe dysplasia; one was carcinoma in situ of the vagina.

Surgery.

Simple excision. Surgery was performed in 17 of 22 patients. Simple excision biopsy for intraepithelial vaginal disease was utilized in 14 of the patients. Eleven patients were sexually active and experienced no dyspareunia. No patients developed stress incontinence from vaginal stenosis. Three of these patients had abnormal Papanicolaou smears, with negative cone biopsies of the cervix. The vaginal lesion was identified with iodine stain and colposcopy.

Vaginectomy. Two patients with large-area lesions involving the entire upper third of the vagina underwent vaginectomy; both have had recurrence of disease. One carcinoma in situ occurred one year after excision biopsy. Vaginectomy and split-thickness skin graft were performed to remove the lesion and maintain sexual function. The other patient developed recurrence 4 years following vaginectomy, and the recurrence was manifested by a pelvic mass which proved at laparotomy to be squamous cell carcinoma. She has had good response to radiation therapy and is alive with disease 1 year following therapy.

Pelvic exenteration. One patient underwent pelvic exenteration 9 years after treatment with radiation and hysterectomy for carcinoma in situ of the cervix. Results of a punch biopsy of a vaginal lesion were reported as invasive disease. The vaginal lesion at the time of exenteration showed only carcinoma in situ of the vagina. This patient died on the fourth postoperative day of pulmonary complications.

Radiation therapy. Four of the 22 patients were treated with intravaginal radiation therapy. Two patients developed vaginal shortening and stenosis, followed by dyspareunia, and have since been treated with estrogen cream and vaginal dilators, with acceptable sexual function. Four patients have remained free of disease.

Chemotherapy. Topical 5-fluorouracil was utilized in one patient, a treatment described by Woodruff and colleagues.[7] This patient developed an abnormal Papanicolaou smear, with a "blush" lesion proved by biopsy to be carcinoma in situ of the vagina. She refused surgical excision of these areas and is free of disease 4 years following topical chemotherapy; Papanicolaou smears have remained negative.

Comment

Many gynecologists and internists feel that Papanicolaou smears are no longer indicated following hysterectomy, especially following hysterectomy for benign disease.[1, 8, 9] Hummer and colleagues[1] pointed out that the patient with an abnormal Papanicolaou smear rarely has any complaints with these lesions. This finding was substantiated in 21 of the 22 cases. Nine of the 22 patients had visible lesions which were noted with careful examination and iodine stains after abnormal Papanicolaou smears. These lesions have been described as "blush" lesions by Gray and Christopherson,[10] who found, by biopsy, that 80% of them were preinvasive.

The average age of patients with carcinoma in situ of the vagina in this series was 53.5 years, which is similar to the findings of Hummer and co-workers.[1] Recent studies in the United States reveal that approximately 0.4% of female genital tract lesions are preinvasive lesions of the vaginal tract.[11] Most authors feel that previous carcinoma in situ of the cervix predisposes the patient to carcinoma in situ of the vagina, and Scales and Hartman[12] feel this multicentric theory is probably true, since the epithelium of the vagina and cervix originates from the urogenital sinus. Carcinoma in situ of the cervix preceded the vaginal lesion in eight of 22 cases (39%) and occurred from 6 months to 10 years after the original surgery. It is not uncommon to find carcinoma in situ of the vagina several years after a hysterectomy for benign disease or after carcinoma in situ of the cervix. Rutledge[3] has reported at least seven cases in which this has occurred up to 22 years following primary surgery. Rutledge feels that patients who wish to maintain sexual activity should have local excision and skin grafts when indicated. Brown and colleagues[13] have found recurrence in patients treated by local radium therapy and feel this is due to "cold spots" caused by rugae of the vagina, thus leading to the opinion that partial vaginectomy is the treatment of choice. The multiple angles created by vaginal rugae make colposcopic evaluation of the vaginal lesion more difficult than that of the smooth surface of the cervix. Preoperative treatment with estrogen creams has been advocated by Gray and Christopherson[10] in the postmenopausal patient. Topical cream reduces atrophic changes, makes the intraepithelial lesion more apparent, and increases vaginal mucosal elasticity.[14]

The problem with scarring and stenosis of the vagina following radiation is not new and certainly not confined to this disease. However, the patients who have radiation as a means of treatment should receive estrogen cream, as well as vaginal dilatation, to prevent stenosis, scarring, and loss of sexual function.[8]

Colposcopy has been very helpful in evaluation of cervical lesions and of some value in vaginal lesions but multiple refractory angles of vaginal rugae make evaluation of invasive vaginal carcinoma inaccurate.

• Other methods of treatment, such as topical 5-fluorouracil cream, cryosurgery, and laser surgery, should be used only in patients who are poor surgical risks or refuse surgery. The importance of total excision of these vaginal lesions cannot be overemphasized for by this method of total removal the depth and extent of penetration of the lesion can be adequately evaluated and inadequate treatment of invasive vaginal disease can be avoided.

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Discussion

Dr. Edward C. Hill, San Francisco, California. It is noteworthy that all but three of the patients in Dr. Oliver's series had previously undergone total abdominal hysterectomy. That almost half of the hysterectomies were done for neoplastic disease of the cervix is not surprising for this places the patient at risk for the subsequent development, or at least the finding, of carcinoma in situ of the vagina. It is quite extraordinary to find carcinoma in situ of the vagina in a patient who has had a hysterectomy for a disease which was ostensibly benign. This raises the question of the need for routine cytologic examination of the vagina in such patients, and Dr. Oliver has recommended that this be done, presumably on an annual basis.

At the University of California, San Francisco, the ratio of vaginal to cervical cancer has been 1:50. Others have found a ratio as high as 1:24. If the risk of cervical cancer in the general female population is approximately 1%, then it can be presumed that the risk of vaginal cancer, at the most, is about 1:2,500.

It has been established that about 750,000 hysterectomies are performed annually in the United States. If 25% of these are done for neoplastic disease, then 562,500 patients per year have hysterectomies for benign disease. At $10.00 per cytologic examination, it would cost a minimum of $25,000 to detect a single case of carcinoma of the vagina by routine cytologic examination in this population. Is this a reasonable cost-benefit ratio?

One must also ask what led to the cytologic examination of the patients in Dr. Oliver's series who had previously experienced hysterectomy for benign disease. He has indicated that six of the 11 patients had visible lesions. Was the smear obtained in each of these cases because of the lesion? It is not clear from the paper what these lesions looked like. Were they the so-called "blush" lesions which he mentioned, or were they areas of leukoplakia? Were they noted by someone whose eye had been trained by colposcopy?

The three patients in this series who had intact uteri were all 30 years of age or younger and cone biopsy of the cervix was done in all because of abnormal cytologic smear. In each instance the cervical cone specimen demonstrated mild dysplasia while the vaginal lesion presented a more marked degree of intraepithelial neoplasia. It appears that these three patients represented cases in which a field of dysplasia was found with the more severe form of the process in the adjacent vagina rather than in the cervix.

All but one of the patients had involvement of the upper third of the vagina. Does this mean that there is some relationship between the development of vaginal neoplasia and the role of the müllerian duct epithelium in the embryologic development of the vagina? Experience with cervical intraepithelial neoplasia and the concept of the expanded transformation zone in diethylstilbestrol-exposed female subjects would lead us to believe so.

Purely out of curiosity, I thought it would be interesting to compare the essayist's series of patients with the experience at the University of California, San Francisco. A review of the 10 years from 1968 through 1977 produced 22 patients with carcinoma in situ of the vagina, ranging in age from 29 to 77 years with an average age of 56.7 years. Twelve of these had prior hysterectomy, nine of which were for malignant disease, primarily of the cervix. In the three patients who had hysterectomy for benign disease, one had carcinoma in situ of the vulva 2 years previously, so she was at risk, and another had worn a Gellhorn pessary for 10 years and had a visible lesion. Of the 10 patients who had not

had prior hysterectomy, 80% had received radiation therapy, primarily for carcinoma of the cervix, from 8 to 29 years prior to the diagnosis of vaginal carcinoma in situ. In the two patients who had not received radiation therapy, one had been treated for carcinoma in situ of the vulva and the other had been receiving immunosuppressive therapy for a kidney transplant and had also been treated for carcinoma in situ of the cervix as well as the vulva. So only two of the 22 patients had carcinoma in situ of the vagina without apparent relationship to neoplasia elsewhere in the reproductive tract and one of these was attributed to the use of a vaginal pessary for many years.

Although our experience differs from Dr. Oliver's, I agree with his conclusions except for his advocation of routine cytologic examinations of the vagina in women who have had hysterectomy for benign disease. An occasional smear, say once every 5 years, ought to suffice. Carcinoma of the vagina in this selected group of patients must be very rare indeed.

DR. JAMES F. NOLAN, Los Angeles, California. Recently we made a study similar to Dr. Oliver's. Our findings were remarkably similar to his, with some minor exceptions which may be worth discussion.

We found some 36 patients who were diagnosed as having vaginal carcinoma in situ in a 22 year period (1955 to 1977). Only four of these patients had no previous gynecologic treatment. Of the 32 treated previously, only six were reported to have benign disease. The remainder had been treated by surgery or radiation therapy for carcinoma of the cervix, either in situ or invasive. The vaginal carcinoma in situ was diagnosed from 1 to 19 years after the original procedure, with an equal distribution of patients before and after 5 years of follow-up. The cause of these new preinvasive lesions remains moot, but continued surveillance in treated patients seems indicated.

As far as treatment of the carcinoma in situ is concerned, there may be some divergence of opinion. Of course, the end results with different modalities are similar and hover at about a 100% success rate. We treated the majority of our patients with local radium implants but were completely successful with all methods used. One patient who received radium developed cystitis and one developed proctitis—both controlled with conservative measures. Previously both had been treated for carcinoma of the cervix with full radiation therapy. One would think the problem of vaginal rugae should be overcome by packing and the fact that gamma radiation doses would not be significantly lowered within a few millimeters of the surface dose. As Dr. Oliver pointed out, the problem of postradiation atresia in sexually active individuals can be countered by measures similar to those used to maintain vaginal patency in the postoperative patients.

At least local radiation treatment is simpler than vaginectomy and was equally effective in our experience.

DR. LEON P. FOX, San Jose, California. Dr. Oliver deserves credit for championing the routine use of the Papanicolaou smear in patients following hysterectomy. We have been doing this in our office since we pioneered cytologic screening in our area in 1952. We have had a similar experience of identifying an occasional malignancy and several cases of dysplasia of the vagina. The numbers are small, but for the person who has the lesions it is a procedure of 100% value. The hysterectomized patient derives several advantages from the smear. It detects disease processes, indicates estrogen levels, and is one of the best incentives for patients to have routine checkups. Misinformed internists, surgeons, and many of our own colleagues are doing an injustice to these patients when they withhold this low-cost valuable service from them.

DR. LEO LAGASSE, Los Angeles, California. We have recently reviewed our experience in 12 patients treated with intravaginal 5-fluorouracil for carcinoma in situ of the vagina. All 12 of these patients responded completely after one to three 2 week periods of therapy. Three patients had recurrences 18 months to 3 years after treatment and all responded to another course of therapy. All were left with normal vaginas afterward. The treatment is very well tolerated. A few patients experienced burning of the vulva or urethra, which was prevented by a barrier-type ointment applied to the vulva before insertion of the 5-fluorouracil cream. It must be emphasized that very careful examination of the vagina with multiple biopsies is necessary to rule out invasive cancer with certainty in these patients. There appears to be a place for 5-fluorouracil in the treatment of vaginal carcinoma in situ. I would suggest it to you as an alternative to surgery or radiation.

DR. WILSON FOOTER, Oakland, California. I have found that approximately one third of the patients that I have seen with this condition have had radiation previously for various conditions, usually of the cervix. One had, as a child, a malignancy of the hip and was given radiation. Approximately one third had previous hysterectomy for a benign condition; the remainder, for malignancy The "blush" type of lesion was found in one patient at approximately 60 years of age. With manipulation there was a little bleeding from it but that was not one of her symptoms. This lesion should be excised, with a wide margin around the lesion, which can be demarcated colposcopically both in the office and by the operating microscope in surgery with Lugol's solution. We use Lugol's solution first and then toluidine blue. We utilize wide margins around and deep into the lesion. There has been no evidence of recurrence in the patient described, who was treated in 1971. She was also treated with dichloroacetic acid, which I have used on a number of cases. If the lesion is not at the apex but down inside the vagina, so that it is not involved with the previous scar from a hysterectomy, we can usually rely upon dichloroacetic acid, as well as excision or 5-fluorouracil to eliminate the condition. However, I have excised those that are at the

apex and those that go out into a dimpling at the side; where there was any shortening of the vagina, a split-thickness graft was utilized. However, in most, the extent of the lesion is such that the vagina is not very much shortened. It has been mainly those having this condition after radiation therapy who had enough shortening that the split-thickness graft was helpful.

DR. EDWIN T. MACCAMY, Seattle, Washington. I would like to ask Dr. Oliver if he has any special technique for obtaining the Papanicolaou smear. Does he just take it across the vaginal vault, as we would with the cervix still present? Apropos of Hill's comment that perhaps a Papanicolaou smear is not needed more often than every 5 years, I would like to describe a particular case to illustrate how long this disease can go on. A patient with a positive Papanicolaou smear, who was treated by cervical conization, had a negative tissue report. She then underwent hysterectomy and the hysterectomy specimen was negative. The general surgeon retired, and she had no further examination for 7 years. She then went to an internist who obtained a Papanicolaou smear, and again it was positive. She had carcinoma in situ of the vagina—a very diffuse carcinoma; still, it was only in situ after at least 7 years.

DR. BOYD C. QUINT, Seattle, Washington. Dr. Oliver mentioned that none of his patients were diethylstilbestrol-exposed infants. Dr. Hill alluded to this as a potential problem. I would just like to underscore that a little. Dr. Staphl, from Marquette University, has pointed out that he is very concerned about the possibility of diethylstilbestrol-exposed babies, the oldest of whom are now something like 27 years old, eventually developing squamous cell carcinoma in the widened transformation zone they have. We may well be sitting on a "powder keg" with these four million or more such exposed young ladies. Unfortunately, those of you who perform colposcopy are well aware of the fact that the usual colposcopic criteria of mosaicism and punctation are of no value in the diethylstilbestrol-exposed subjects—they all have these in the transformation zone and thus must be evaluated by Papanicolaou smear.

DR. OLIVER (Closing). One of the questions that Dr. Hill asked was what led to the Papanicolaou smear? This was just done on a routine yearly basis when the patient came in for her annual examination. Dr. MacCamy asked about technique: We just scrape the vagina as we do the cervix and there is no special technique involved.

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Does adoption affect subsequent fertility?

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A hypothesis derived from the old wives' tale that adoption increases subsequent fertility was tested by analysis of follow-up data obtained from 895 couples who were "at risk" of pregnancy and of adoption after they had registered in the Stanford Infertility Clinic between 1963 and 1977. Of the 767 couples who did not adopt, 329 later conceived; of the 128 who did adopt, 41 later conceived. Simple comparison of the percentages or, indeed, of the life tables suggests reduced fertility after adoption. However, this is probably a spurious effect related to a number of factors which differ between two groups. These differences were controlled in the statistical analysis by methods which take into account the length of time each couple was at risk of either conception or adoption and the presence or absence of explanatory variables. The relative risk of conception estimated by the Cox model was not significantly different from 1 and the Mantel-Haenszel statistic ($m = -0.208$) indicates no significant difference in subsequent conception rates between adoptive and not-adoptive couples. The same methods were used to control for seven covariates, including age and duration of infertility, which could affect conception rates. In each instance, the estimate of relative risk of conception for adoptive versus not-adoptive couples was not significantly different from 1. Therefore, our data do not support the hypothesis that adoption affects subsequent fertility. (AM. J. OBSTET. GYNECOL. 134:138, 1979.)

EVEN THOUGH THE NUMBERS of babies available for adoption have been reduced in recent years by marked changes in society's attitudes toward contraception, abortion, and single parenthood, about 150,000 babies are adopted each year in the United States. Quite a few adoptive parents and at least some of their physicians hope that the adopted child will serve as a "fertility charm." The concept that adoption may be a cure for infertility is prevalent not only among the laity but even in medical circles.

In this study data from a large sample of infertile couples, studied and followed up in a uniform manner, have been analyzed using modern statistical methods in an attempt to answer the question: Does adoption affect subsequent fertility?

Methods

Data collection and definitions. Couples who registered in the Stanford Infertility Clinic between January 1, 1963, and the closing date of this study, December 31, 1976, form the study group. The following were excluded: those who were seen for one-visit consultation, those lost to follow-up immediately after registration, and those who were known not to be "at risk" of conception at the time of registration because of an existing, but undiagnosed, pregnancy or because of known factors which rendered them completely sterile. The tests included in the infertility investigation and the methods for data collection and tabulation are described in a previous paper.[6] Information about adoption, pregnancy, contraception, divorce, etc., was obtained from couples through follow-up visits or letters.

Until they had actually adopted, a couple was considered in the not-adoptive group. Thereafter, they were included in the adoptive group. Only first adoptions or conceptions following registration were considered. Couples were defined as adoptive only if the adoption occurred between registration and withdrawal from follow-up for any reason. Those who adopted before registration are included in the not-adoptive group. Routine follow-up procedures cease when it is learned that a couple has conceived or has withdrawn permanently from the risk of pregnancy by contraception, sterilization, divorce, etc. Therefore, our data are incomplete about adoption subsequent to a pregnancy or after sterilization procedures including hysterectomy.

From the Departments of Gynecology and Obstetrics and of Statistics, Stanford University.

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Table I. Distribution of pregnancies among adoptive and not-adoptive couples in five studies. An estimated risk ratio less than 1 indicates that couples who adopted have a lower risk of pregnancy

Study	Year	No. of couples				Estimated risk ratio	Chi-square value
		Pregnant		Not pregnant			
		A. Adoptive	B. Not-adoptive	C. Adoptive	D. Not-adoptive		
Rock et al.[11]	1965	57	40	192	73	0.65	6.2*
Weir and Weir[12]	1966	32	44	165	197	0.89	0.3
Humphrey and McKenzie[3]	1967	7	76	52	81	0.25	24.2†
Arronet et al.[1]	1974	26	264	107	136	0.30	86.8†
Present study		41	329	87	438	0.75	5.3*

*$p < 0.05$; for 1 degree of freedom χ^2 ($p = 0.05$) = 3.8.
†$p < 0.01$; for 1 degree of freedom χ^2 ($p = 0.01$) = 6.6.

Table II. Distribution of conceptions and other events between adoptive and not-adoptive couples

	Status at last contact				Total
	Pregnant	Known not pregnant at close of study	Withdrawn from risk of pregnancy	Lost to follow-up	
Adoptive	41	44	27	16	128
Not-adoptive	329	180	199	59	767
Total	370	224	226	75	895

Such cases are included in the not-adoptive group and considered withdrawn from the study before adoption. These restrictions lead to an underestimation of adoption rates but do not affect calculation of conception rates.

The time interval from registration until each event (conception, adoption, loss to follow-up, withdrawal from the risk of conception) was calculated. The interval to adoption was determined by the arrival of the adopted child in the home rather than by the date of application for adoption. On the other hand, the interval to conception was determined by the last menstrual period, not by the date of delivery. The interval to withdrawal from the study because the couple was found to have a condition which made conception impossible, e.g., azoospermia or complete tubal occlusion, was determined by the date of diagnosis.

Whether the explanatory variable listed in Table III was present or absent was determined at the time of registration with the exception of therapy which was coded at the end of the follow-up.

The relevant medical literature of the past 20 years was reviewed and reports were selected which provided sufficient data for construction of a 2 by 2 contingency table. The estimated relative risk of conception was calculated using the formula $(A/A + C) \div (B/B + D)$ where A, B, C, and D are as defined in Table I. A chi-square test of independence was done for each row of the table with no correction for continuity.

Statistical methods. With the use of the intervals between registration and each of the ensuing events, life tables for the various groups were calculated with computer programs. In these calculations the three censoring events, loss to follow-up, withdrawal because of sterility, and survival to the close of the study, are handled in a similar fashion. The life tables were calculated using the formulas on pages 464 and 477 of Kaplan and Meier.[5] The overall significance test statistic M was calculated by the formulas on page 734 of Mantel and Haenszel[9] and page 79 of Hyde.[4] The hazard function and estimate of relative risk were calculated by the method on page 189 of Cox.[2] Analysis of the effect of the covariates listed in Table III was by the global significance test on page 191 of Cox. A more complete exposition for the statistician of the methods used in this study is in preparation.[8]

Results

Of 1,201 couples who registered in the clinic during the time of this study, 76 were known at registration to be not at risk of pregnancy either because, in 58, an undiagnosed pregnancy existed or because, in 18, an untreatable condition which rendered the couple sterile was known. An additional 232 patients were not followed up beyond the day of registration because they were seen for consultation only or were immediately lost to follow-up. Of the 895 couples remaining in the study, 370 (41%) did conceive and 525 did

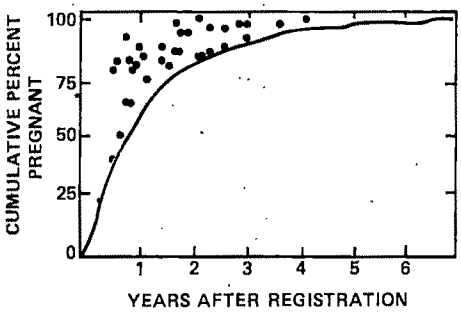


Fig. 1. Interval between registration and conception for 370 couples who conceived. Points which indicate couples who had adopted and conceived are plotted at a level on the abscissa corresponding to that couple's place on the curve. Thus, the horizontal distance between a point and the curve is the interval between adoption and conception.

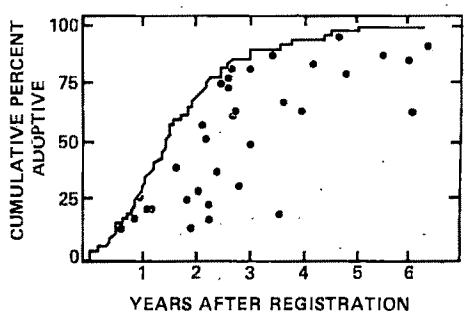


Fig. 2. Interval between registration and adoption for 128 couples who adopted. Points which indicate couples who had adopted and conceived are plotted as in Fig. 1. The horizontal distance between a point and the curve is the interval between adoption and conception.

not. At some time after registration and before conceiving 128 (14%) adopted. Of these adoptive couples 41 (32%) subsequently conceived. According to the chi-square test of independence, the estimated risk ratio 0.75 (adoptive/not adoptive) is significantly different ($p < 0.05$) from unity (Table I). Results of previous studies of the question of the effect of adoption on fertility are also listed in Table I.[1, 3, 11, 12]

The numbers of those in the study who were observed until the closing date, withdrawn because of sterility, etc., or lost to follow-up are listed in Table II.

The interval between registration and conception for the 370 couples who conceived is shown in Fig. 1. The median interval to conception was 0.81 years. The interval between registration and adoption for the 128 adoptive couples is shown in Fig. 2. The median interval to adoption was 1.40 years. The intervals between adoption and conception for couples who adopted and later conceived are also illustrated in Figs. 1 and 2. The median interval was 1.0 years; the range, 0.1 to 3.6 years; the mean, 1.48 years; and the standard deviation, 1.86 years.

Life-table estimates of the proportion of couples who had conceived at intervals after registration are shown in Fig. 3. We estimate that had all not-adoptive couples been observed for 5 years, 69% would have conceived. The corresponding points are 35% for adoptive couples and 63% for all couples. The Mantel-Haenszel statistic $M = -0.208$ does not differ significantly from 0, indicating that the relative risk of conception (adoptive/not-adoptive) does not differ significantly from 1.

The effect on the relative risk of conception for adoptive versus not-adoptive couples and for couples with seven explanatory variables is shown in Table III. Using life-table methods of analysis we found a significant difference in conception rates between the

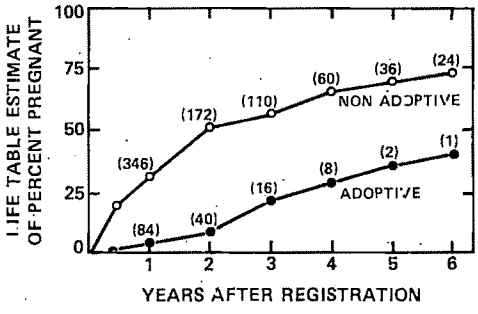


Fig. 3. Proportion of pregnancies achieved at various intervals after registration estimated by life-table methods. The number of couples still at risk of conception and under observation at each year after registration is indicated on the lines.

four groups (adoptive, not-adoptive, and the two strata of the covariates) for two covariates, duration of infertility and age of the wife at the time of registration. In none of the 14 comparisons in which the covariates were controlled did the difference in estimated risk ratio (adoptive/not-adoptive) reach the 0.05 level of significance. In one instance, that of a wife over 30 years old at registration, it approached this level.

Comment

A challenging aspect of the analysis of these data was the change in status of couples during the course of follow-up. Since many infertile couples evidence a fluctuating interest in adoption, we could not determine accurately which couple would and which would not become an adoptive couple until adoption had occurred. Adoptive couples must remain infertile at least long enough to adopt (Figs. 1 and 2). An analogous situation in which the treatment status changes during the course of follow-up is present in studies of heart transplant patients who are kept under observation until a suitable donor is found, at which time they re-

Table III. Effect of seven covariates on the risk ratio for conception (adoptive versus not-adoptive couples). An estimated risk ratio less than 1 and a negative Mantel-Haenszel statistic, M, indicate a lower risk of pregnancy for adoptive couples. The effect of the covariate on the risk of pregnancy was also estimated

	No. of couples				*Effect of variables*		
						Adoption	
Covariates	*Pregnant and adoptive*	*Pregnant and not-adoptive*	*Not pregnant and adoptive*	*Not pregnant and not-adoptive*	*Covariate: significance test (Cox)*	*Estimated risk ratio (Cox)*	*Significance test (M)*
Years of infertility:							
≤ 2.9 yr.	27	211	42	199	22.0*	0.78	−1.08
≥ 3.0 yr.	12	118	41	242		0.81	−0.70
Age of wife:							
20-29.9 yr.	35	221	58	283	8.8*	1.08	+0.32
30-39.9 yr.	4	96	24	136		0.46	−1.85†
Semen analysis:							
Normal	19	159	36	181	6.8	0.83	−0.72
Abnormal	1	31	9	73		0.53	−0.69
Tubal or peritoneal test:							
Normal	4	88	28	104	5.8	0.96	−0.13
Abnormal	20	116	44	166		1.06	+0.22
Menstruation:							
Regular	21	208	52	313	1.3	0.79	−0.95
Absent/irregular	18	122	31	126		0.95	
Parity:							
Never pregnant	30	199	60	259	1.5	0.99	−0.35
Previous term birth	4	74	11	119		0.56	−1.12
Therapy:							
Specific	31	212	37	306	1.1	0.80	−0.92
None or nonspecific	18	117	54	132		0.88	−0.42

*$p < 0.05$; with 3 degrees of freedom, χ^2 ($p = 0.05$) = 7.8.
†$p \simeq 0.06$; M ($p = 0.05$) = 1.96.

ceive the transplant. We approached this problem in a way previously used for analysis of such data[4] by counting couples adopting during the course of the follow-up in the not-adoptive group until the day of the adoption and thereafter in the adoptive group.

Simple comparison of life tables for the adoptive and not-adoptive groups (Fig. 3) is definitely misleading if one fails to take into account possible reasons for these differences. The first was noted above—couples who adopt must remain infertile at least until the adoptive child is in their home; several other reasons will be discussed below.

Analysis of the entire observation period is necessary to estimate the relative risk of conception for couples in the two groups and to estimate the significance of the difference of this ratio from unity. Statistical methods used to estimate the relative risk and to test whether it differs significantly from 1 may be thought of as derived from the familiar chi-square test of independence used with a 2 by 2 contingency table. For this analogy one can imagine constructing a 2 by 2 contingency table for each discrete interval on the life-table graphs for comparison of the two groups. From the observed number in each of the four cells and from the marginal totals, one then determines the expected number for each cell. By passing an observation window across the entire life-table graph from the starting point and collecting the chi-square statistics as one goes, one can derive a summary chi-square statistic which would measure the significance of the difference between the two curves. The p value obtained could be considered the significance level at which one could just reject the null hypothesis that there is no difference in risk between the two groups.

A related statistic, M, proposed by Mantel and Haenszel to test the overall significance of such differences, is obtained by relating the sum of the differences in the individual cells to the sum of the variances.[9] For this study, we calculated the square root of this Mantel-Haenszel summary chi-square statistic (Table III).[4] This statistic has a normal rather than a chi-square distribution and the sign indicates the direction of the difference between the groups. A positive M indicates a greater chance of conception for adoptive couples; a negative M indicates a lesser chance, and an M of 0 indicates no difference. The M statistic calcu-

lated from our data was −0.208, a value which does no- differ significantly ($p = > 0.05$) from 0. In other words, the relative risk of pregnancy for those who hac adopted compared with those who had not did not differ significantly from 1.

Because of differences in sampling and censoring between the two groups the estimate of the relative risk itself was made by the regression method of Cox.[2] Discussion of the advantages and disadvantages of alternative methods of estimating risk ratios is beyond the scope of this paper. A recent review in the *British Journal of Cancer* discusses the general principles underlying these statistical methods in terms easily understood by medical investigators who are not familiar with statistical theory.[10]

We used the estimates of relative risks and their significance to identify and correct for two potential problems, one of which occurs late in the follow-up period and the other early in the follow-up period.

Late in the follow-up period, conception is less likely but adoption is still likely (Figs. 2 and 3). Those who adopt late are likely to be among the less fertile simply because couples then remaining under study are less likely to conceive. As shown in Fig. 3, the conception rate curve flattens out late in the follow-up period. The couples are now older, have been infertile longer, and have failed to prove themselves mildly infertile by conceiving early in follow-up. The methods of life-table analysis which were used in this study minimize this effect since comparisons of the risks of conception are made at equivalent times after registration.

Another problem in interpretation of the data is present early in the follow-up period, soon after the diagnostic survey. The least fertile are more likely to adopt then because couples judged to have a poor prognosis for conception are usually advised against delaying serious consideration of adoption.[7] Those who appear to have a good prognosis are not so advised and often do delay their decision at least for a time. By separate analysis of data for couples with or without various factors which might adversely affect fertility, we have attempted to identify and correct for variables which might affect the overall risk ratio. We determined the effect of the presence or absence of seven such covariates on the relative risk of conception for adoptive and not-adoptive couples. The absence of a significant difference in relative risk in any of these strata strengthens the conclusion reached about the total group.

Relative risks determined from a 2 by 2 contingency table are subject to the sources of error which we have discussed above. However, we could find only four publications (Table III) which provided enough data for even that type of analysis of overall conception rates comparing those who had adopted versus those who had never adopted.[1, 3, 11, 12] Additional comparison of these studies is impossible since each author used a different method of case selection and analysis. These previous studies have failed to end speculation about the therapeutic value of adoption for infertility. Other reports which merely related anecdotes or postulated explanations for the quasimystical effect of adoption will not be cited.

The practical difficulties of conducting an experiment, for example, one in which groups from a uniform population of infertile couples are randomly assigned to adopt or not to adopt, make it apparent that the question may never be finally settled. We considered the present study to be much more likely to provide an answer since the methods of statistical analysis controlled for changing treatment status during follow-up, for differences in the intervals between registration and adoption or conception, and for the presence or absence of several explanatory variables. This study does not provide support for the concept that adoption affects subsequent fertility.

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Discussion

DR. RALPH C. BENSON, Portland, Oregon. The notion that adoption enhances fertility is shrouded in the mists of time. Certainly this belief has often been the sustaining hope in a barren marriage. Be this as it may, physicians have invoked this possibility as an escape after discouraging infertility study and treatment. In any event, like other old wives' tales, we should know whether this concept is true or false. Hence this investigation is a quest for truth or lack thereof.

Assuming that this hypothesis is correct, how could adoption improve fertility? There are a number of possibilities:

1. Divine intervention may result in pregnancy. Genesis 25:21 records the earliest case, "And Isaac prayed unto the Lord for his wife because she was barren; and the Lord granted his prayer and Rebeckah his wife conceived." How often such an invocation has been successful will never be known. Prayer is one approach to the cure of infertility but the Lord helps those who help themselves.

2. Therapeutic corrections may require a longer time than originally projected to become effective. Thus the couple may have become adoptive parents by the time pregnancy occurs.

Although one year usually is considered to be a reasonable period of time for pregnancy to ensue, a diminishing number of pregnancies will be recorded for months or even years later. If significant factors persist despite treatment, e.g., peritubal adhesions or oligospermia, more time may be necessary for pregnancy to occur.

Psychosomatic factors which may cause infertility are slow to resolve—with or without psychotherapy. For the man, these problems include functional impotence, premature ejaculation, or avoidance of coitus. Psychological improvement may lead to increased frequency of successful intercourse. For the woman, disturbances of ovulation and lack of disposition for intercourse during the known fertile period may be reversed. If one accepts the explanation that, in women, psychic conflicts lead to hormone disturbances via the hypophyseal-diencephalic system which cause infertility, the wife may ultimately "settle down" and reproduce. Unfortunately, evidence of this is fragmentary and uncontrolled. Nevertheless, if resolution does occur, it is more likely to be late than early because of the complexities involved.

Evidence that adoption does affect subsequent fertility is not persuasive. Scattered reports, most of which are anecdotal, suggest some benefit. However, clinical opinion is almost equally divided on this view. The limited number of studies assessed by Dr. Lamb and his co-workers have not proved their thesis, as he has indicated.

In this study, the authors have studied and treated a large number of patients and their follow-up is impressive. Moreover, they have gone to considerable lengths to be "fair" in their assumptions and comparisons. For example, they did not emphasize the fact that those patients who did adopt achieved fewer pregnancies than those who did not adopt (42.8% versus 32.0%). Their generous comment suggested that this is a "spurious" effect.

Dr. Lamb and his associates have estimated that had all not-adoptive couples been followed up for 5 years, 69% would have conceived. The corresponding points are 35% for adoption and 63% for all couples. Again adoption seems to have lost its reputed impact.

Certain guidelines must be made and often these are arbitrary, for example, "Until they had actually adopted, a couple was considered in the not-adoptive group." Adoption is a slow process. Hence this rule would seem to handicap the adoptive group to some extent. In addition, a small number of adoptions were arranged before registration and these women were included in the not-adoptive category. Despite these positive decisions, it is likely that such restrictions lead to underestimates of adoption rates but do not affect the calculation of conception rates.

Be this as it may, I am bothered by the implication that adoption could be arranged promptly so that the woman would quickly pass to a new group. For example, it is stated, "Late in the follow-up period, conception is less likely and adoption is more likely." Also (later), "The least fertile are more likely to adopt early than late because couples judged to have a poor prognosis for conception are usually advised against delaying serious consideration of adoption." This suggests that adoption was a prompt achievement. How often and how soon was adoption accomplished? Years may pass in Oregon before adoption is possible because of the considerable demand and relatively few children available for adoption.

On a positive note, I am most impressed by the elegant statistical methods of evaluation employed. The control of seven covariates which could affect the conception rate should be more than ample and the conclusions are most reasonable and convincing.

The authors did not answer their original question, "Does adoption affect subsequent fertility?" with one word. Their scholarly conclusion is that their study does not provide support for this concept. Nonetheless, for clinical purposes I believe that we can now state categorically that fertility is *not* enhanced by adoption.

DR. WILLIAM O. THOMAS, JR., Portland, Oregon. The point I will make here is possibly more philosophical than scientific. I think that all of us have had the impression, over the years, that adoption does make a difference in these couples. However, as mentioned by Dr. Benson, it seems to me that the only possible situation where adoption could have any effect would be in the couple in whom the psychosomatic

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factors predominate. By that I mean that obviously, if there is extensive tubal damage or other organic pathology in the woman, or any severe pathology as far as the man is concerned, adoption will not have any effect either way. Therefore, I would be most interested in patients in whom all pathology had been completely ruled out and only the psychosomatic factors were to be dealt with, and then the effect of adoption on that group could be determined. With my simple mathematics, I still come up with the fact that of those who did not adopt, 42% conceived, and of those who did adopt, only 32% conceived. But I will admit, Dr. Lamb, that this was a masterful presentation on how to explain that difference away.

DR. EUGENE C. SANDBERG, Stanford, California. I would like to mention one variable that appears not to have been considered, the availability of an infant for adoption. During the years in which these couples were collected and studied, there was a sharp and steady decline in the number of adoptable infants. Consequently, a free selection by the couples of their category, adoptive or not-adoptive, was not possible. It may be that some couples were forced into the not-adoptive group even though their adoptive attitude and psychological makeup (whatever effect this might have on fertility) more closely paralleled those of couples in the adoptive group.

DR. LAMB (Closing). Dr. Benson expressed concern about our analytic model in which subjects were changed from the control (not-adoptive) to the treatment (adoptive) group during the course of the follow-up. A similar model had been developed for study of patients being considered for a heart transplant. They waited an unpredictable period until a donor became available. Those who have a transplant then changed treatment status. Those who died before a donor was found served as the control group.

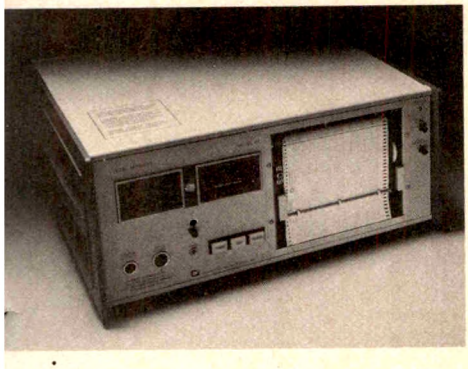
We have difficulty identifying a group with unexplained infertility in whom no organic disorder is present. After thorough investigation of both partners, including routine pelvic endoscopy, we usually find one or more factors which reduce fertility to one degree or another. When we restrict analysis to a group in which none had any one of several combinations of the factors listed in column 2 of Table III, the number of cases remaining is too small to allow meaningful comparisons.

During the interval 1963 to 1976 when intake for this study occurred, the number of infants relinquished for adoption in California fell from about 12,000 to about 3,000. Had we asked the question, "Does the advice to adopt or the desire to adopt affect subsequent fertility?" this fourfold reduction in babies adopted would certainly have a bearing. This was one reason why we chose to ask the question, "Does adoption (bringing the child into the home) affect subsequent fertility?"

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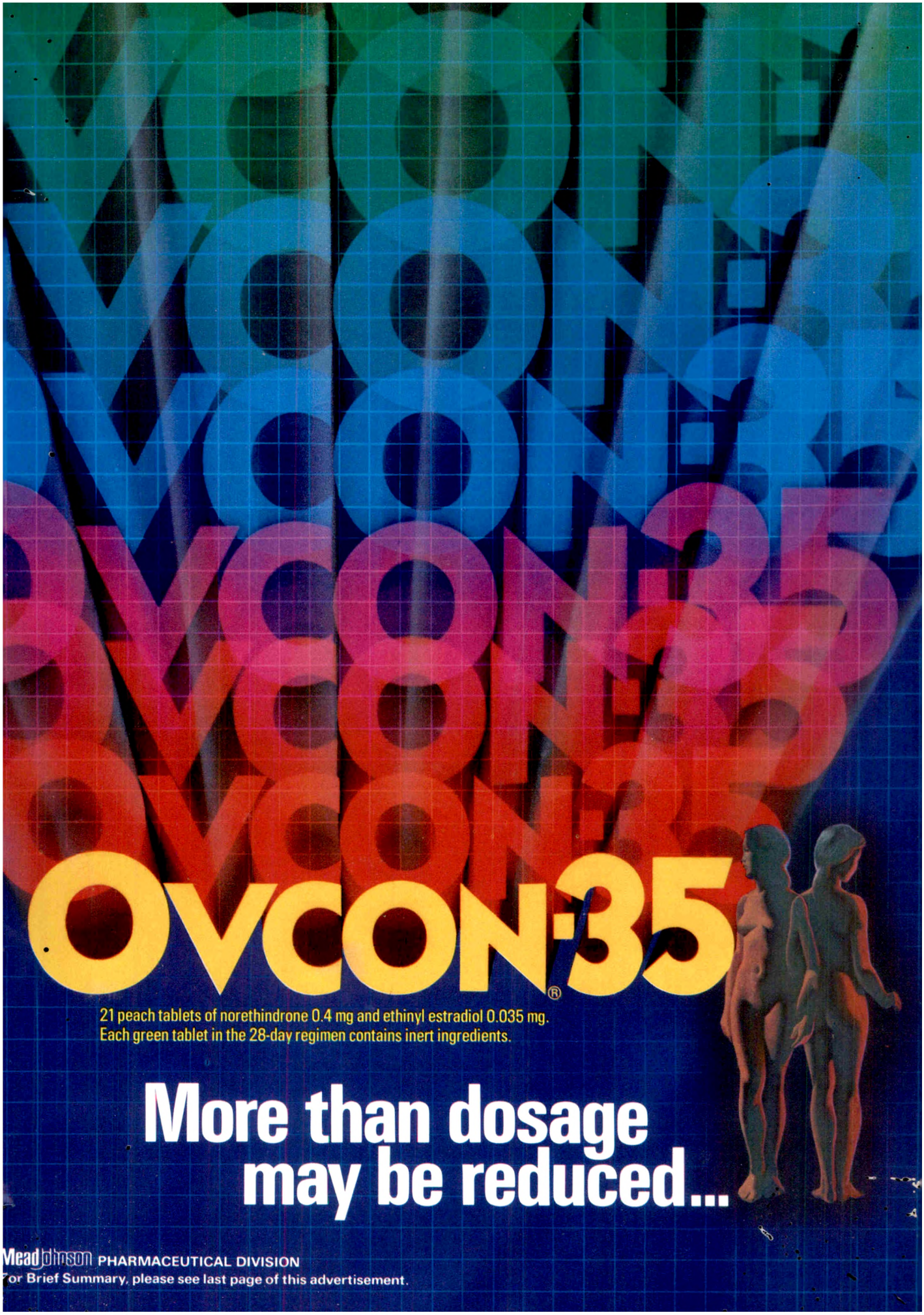
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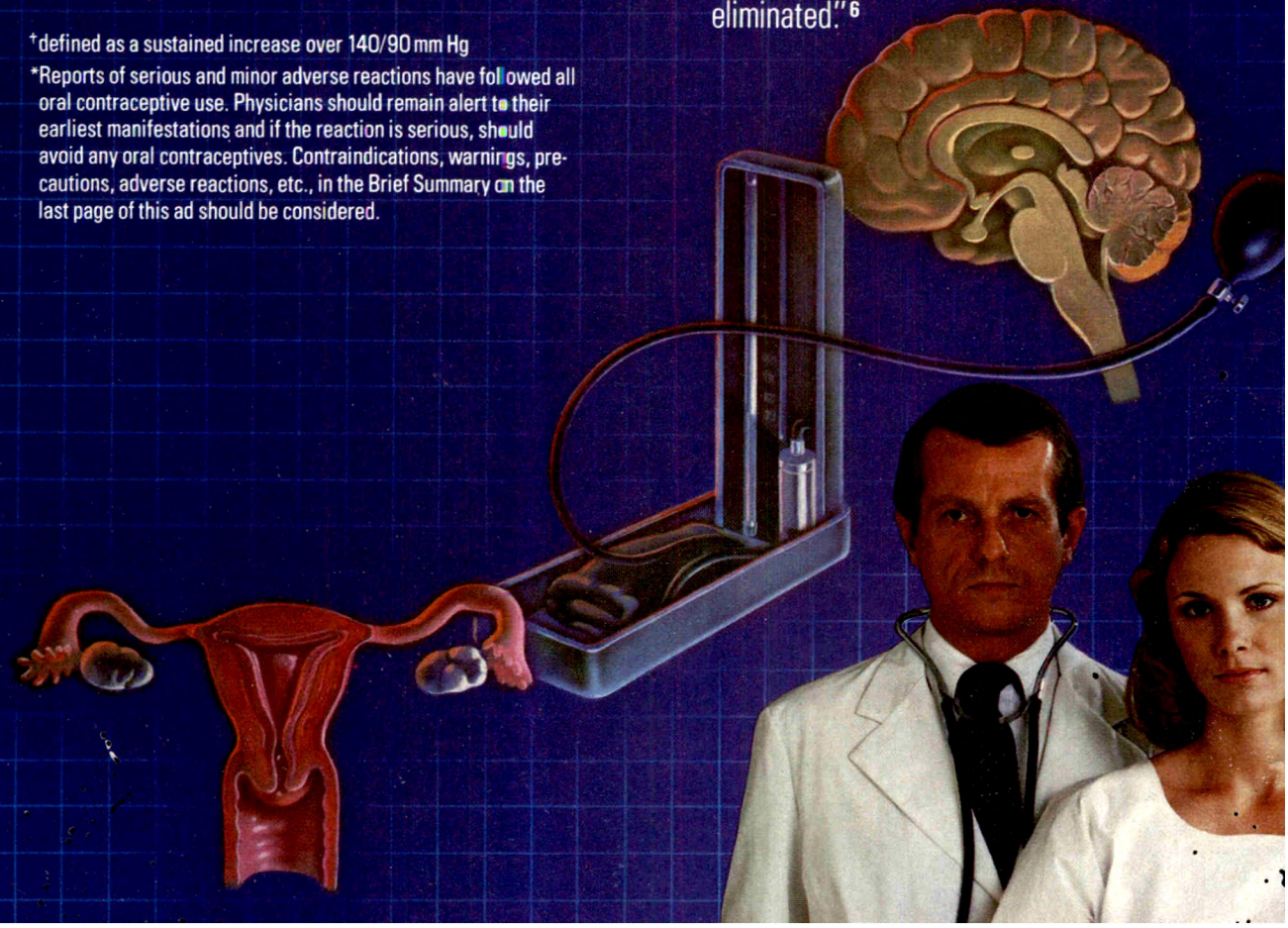
- No hypertension developed in 564 normotensive women during 44 months of one study[5]
- No hypertension was observed in 1,925 of 1,970 women during original clinical experience[4]
- Blood pressure did not increase during 8–18 months of OVCON-35 therapy in four women who were initially hypertensive[5]
- Eighty-four women with histories of toxemia of pregnancy showed no significant differences in blood pressure from 480 women with normal pregnancy histories[5]
- Prevalence of hypertension increases with longer oral contraceptive use and age

†defined as a sustained increase over 140/90 mm Hg

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2 No significant adverse changes in weight, plasma insulin levels, blood glucose values, or fasting triglyceride and cholesterol levels in a preliminary prospective study[6,7]

"Although these data are very preliminary in that they represent only a small number of women (seven) treated for only a short period of time (6 months), they are exciting, for they suggest that perhaps oral contraceptive development has reached a stage where some of the adverse effects have been greatly reduced or eliminated."[6]



and reduced dosage[4-6]

3 OVCON-35 appears to permit prompt return of endometrial function[5]

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Indications and Usage: Ovcon is indicated for the prevention of pregnancy. Some combination products containing 35 mcg. or less of ethinyl estradiol report slightly higher pregnancy rates than are reported for the higher dose combination products.

Contraindications: Oral contraceptives should not be used in women with any of the following conditions: 1) Thrombophlebitis or thromboembolic disorders. 2) A past history of deep vein thrombophlebitis or thromboembolic disorders. 3) Cerebral vascular or coronary artery disease. 4) Known or suspected carcinoma of the breast. 5) Known or suspected estrogen dependent neoplasia. 6) Undiagnosed abnormal genital bleeding. 7) Known or suspected pregnancy.

Warnings:

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. Women who use oral contraceptives should be strongly advised not to smoke. Use of oral contraceptives is associated with increased risk of several serious conditions, including thromboembolism, stroke, myocardial infarction, hepatic adenoma, gallbladder disease, hypertension. Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks.

1) *Thromboembolic Disorders and Other Vascular Problems.* An increased risk of thromboembolic and thrombotic disease associated with use of oral contraceptives is well established. Three principal studies in Great Britain and three in the United States have demonstrated an increased risk of fatal and nonfatal venous thromboembolism and stroke, both hemorrhagic and thrombotic. These studies estimate that users of oral contraceptives are 4 to 11 times more likely than nonusers to develop these diseases without evident cause. In a study of cerebrovascular disorders in women with and without predisposing causes, it was estimated that the risk of hemorrhagic stroke was 2.6 times greater than nonusers and the risk of thrombotic stroke was 4 to 9.5 times greater. An increased risk of myocardial infarction associated with the use of oral contraceptives has been reported. Studies conducted in the United Kingdom found that the greater the number of underlying risk factors for coronary artery disease (cigarette smoking, hypertension, hypercholesterolemia, obesity, diabetes, history of preeclamptic toxemia) the higher the risk of developing myocardial infarction, regardless of whether the patient was an oral contraceptive user or not. Oral contraceptives, however, were found to be a clear additional risk factor. In terms of relative risk, it has been estimated that oral contraceptive users who do not smoke (smoking considered a major predisposing condition to myocardial infarction) are about twice as likely to have a fatal myocardial infarction compared to nonusers who do not smoke. Oral contraceptive users who smoke have about a 5-fold increased risk of fatal infarction compared to users who do not smoke but about a 10- to 12-fold increased risk compared to nonusers who do not smoke. The amount of smoking is a very important factor. British investigators concluded that the risk of thromboembolism including coronary thrombosis is directly related to the dose of estrogen used in oral contraceptives; preparations containing 100 mcg. or more of estrogen were associated with a higher risk of thromboembolism than those containing 50-80 mcg. of estrogen. The relative risk of thromboembolic disease associated with progestin-only oral contraceptives has not been determined. Cases of thromboembolic disease have been reported in women using progestin-only products, and they should not be presumed to be risk-free. The overall excess mortality rate annually from circulatory diseases for oral contraceptive users was estimated to be 20 per 100,000 (ages 15-35: 5/100,000; ages 35-44: 33/100,000; ages 45-49: 140/100,000); the risk being concentrated in older women, in those with a long duration of use, and in cigarette smokers. The highest risk was found in heavy cigarette smokers (15 or more cigarettes per day) who used oral contraceptives and were aged 40 or older. Women who smoke should be advised not to use oral contraceptives. The use of oral contraceptives in women over age 40 with other risk factors is not recommended. The mortality associated with all of the methods of birth control is low compared to the risk of childbirth, with the exception of oral contraceptive users who smoke and are over age 40. The lowest mortality is associated with the condom or diaphragm backed up by early abortion. The risk of thromboembolic and thrombotic disease associated with oral contraceptives increases with age after approximately age 30 and for myocardial infarction is further increased by hypertension, hypercholesterolemia, obesity, diabetes, or history of preeclamptic toxemia, and especially by cigarette smoking. The physician and the patient should be alert to the earliest manifestations of thromboembolic and thrombotic disorders (e.g., thrombophlebitis, pulmonary embolism, cerebrovascular insufficiency, coronary occlusion, retinal thrombosis and mesenteric thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately. If feasible, oral contraceptives should be discontinued at least 4 weeks before surgery of a type associated with an increased risk of thromboembolism or prolonged immobilization. 2) *Ocular Lesions.* There have been reports of neuro-ocular lesions such as optic neuritis or retinal thrombosis associated with the use of oral contraceptives. Discontinue the medication if there is unexplained sudden or gradual partial or complete loss of vision; sudden onset of proptosis or diplopia; papilledema; or retinal vascular lesions; and institute appropriate diagnostic and therapeutic measures. 3) *Carcinoma.* Long term administration of either natural or synthetic estrogen in certain animal species increases the frequency of carcinoma of the breast, cervix, vagina and liver. In humans, one study investigated the first 21 cases of endometrial adenocarcinoma in women on oral contraceptives reported to a registry. Of those women without predisposing risk factors for this disease, nearly all occurred in women who had used a sequential oral contraceptive. No evidence has been reported suggesting an increased risk of endometrial cancer in users of conventional combination or progestin-only oral contraceptives. No increase in breast cancer in women taking oral contraceptives has been reported although one study reported an increased risk of breast cancer in subgroups of women treated using oral contraceptives with documented benign breast disease. There is at present no confirmed evidence from human studies of an increased risk of cancer associated with oral contraceptives. Close clinical surveillance of all women taking oral contraceptives is essential. In all cases of undiagnosed persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be taken to rule out malignancy. Women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease or abnormal mammograms should be monitored with particular care if they elect to use oral contraceptives. 4) *Hepatic Adenoma.* Benign hepatic adenomas have been found to be associated with the use of oral contraceptives. One study reported a higher risk associated with oral contraceptive formulations with high hormonal potency. Although benign and rare, hepatic adenomas may rupture and may cause death through intra-abdominal hemorrhage. This has been reported in short term as well as long term users of oral contraceptives. Two studies relate the risk with duration of contraceptive use: the risk being much greater after 4 or more years of oral contraceptive use. While hepatic adenoma is a rare lesion, it should be considered in women presenting abdominal pain and tenderness, abdominal mass, or shock. A few cases of hepatocellular carcinoma have been reported in women taking oral contraceptives. The relationship of these drugs to this type of malignancy is not known at this time. 5) *Use in Pregnancy, Birth Defects in Offspring and Malignancy in Female Offspring.* Fetal abnormalities have been reported to occur in the offspring of women who have taken progestogens and/or estrogens during pregnancy. It has been shown that females exposed in utero to diethylstilbestrol, a nonsteroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare. A high percentage of such exposed women (30% to 90%) have been found to have epithelial changes of the vagina and cervix. Although these changes are histologically benign it is not known whether this condition is a precursor of vaginal malignancy. Male children so exposed may develop abnormalities of the urogenital tract. Similar data are not available with the use of other estrogens but it cannot be presumed that they would not induce similar changes. The data suggest that the risk of limb reduction defects in exposed fetuses is somewhat less than 1 in 1000 live births. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications and there is no evidence from well-controlled studies that progestins are effective for these uses. Increases in chromosomal aberrations have been reported in women who become pregnant soon after ceasing oral contraceptive therapy. Embryos with these anomalies are virtually always spontaneously aborted. Whether there is an overall increase in spontaneous abortion of pregnancies conceived soon after stopping oral contraceptives is unknown. It is recommended that for any patient who has missed two consecutive periods, pregnancy should be ruled out before continuing the contraceptive regimen. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at the time of the first missed period and further use of oral contraceptives should be withheld until pregnancy has been ruled out. If pregnancy is confirmed the patient should be apprised of the potential risks to the fetus and the advisability of pregnancy continuation should be discussed in light of these risks. It is also recommended that women who discontinue oral contraceptives with the intent of becoming pregnant use an alternate form of contraception for a period of time before attempting to conceive. Many clinicians recommend three months. Administration of progestin-only or progestin-estrogen combinations to induce withdrawal bleeding should not be used as a test for pregnancy. 6) *Gall Bladder Disease.* Studies have reported an increased risk of surgically confirmed gallbladder disease appearing after one year of oral contraceptive use and doubling of the risk after 4 or 5 years of use. 7) *Carbohydrate and Lipid Metabolic Effects.* A decrease in glucose tolerance has been observed in a significant percentage of patients on oral contraceptives. For this reason, prediabetic and diabetic patients should be carefully observed while receiving oral contraceptives. Increased serum levels of triglycerides and total phospholipids have been observed in oral contraceptive users. The clinical significance of this observation is unknown at this time. 8) *Elevated Blood Pressure.* An increase in blood pressure has been reported in women receiving oral contraceptives. The prevalence of hypertension in oral contraceptive users may be no higher than nonusers in the first year of oral contraceptive use but increases with longer exposure and in the fifth year of use is two and one-half to three times the reported prevalence in the first year. Women who previously had hypertension during pregnancy may be more likely to develop elevation of blood pressure when given oral contraceptives. 9) *Headaches.* The onset or exacerbation of migraine or development of headache of a new pattern which is recurrent, persistent or severe, requires discontinuation of oral contraceptives and investigation of the cause. 10) *Bleeding Irregularities.* Breakthrough bleeding, spotting and amenorrhea are frequent reasons for patients discontinuing oral contraceptives. In breakthrough bleeding, as in all cases of irregular bleeding from the vagina, nonfunctional causes should be borne in mind. In undiagnosed persistent or recurrent abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy. If pathology has been excluded, time or change to another formulation may solve the problem. Changing to an oral contraceptive with a higher estrogen content, while potentially useful in minimizing menstrual irregularity, should be done only if necessary since this may increase the risk of thromboembolic disease. Women with a past history of oligomenorrhea or secondary amenorrhea or young women without regular cycles may have a tendency to remain anovulatory or to become amenorrheic after discontinuation of oral contraceptives. Women with these preexisting problems should be advised of this possibility and encouraged to use other contraceptive methods. 11) *Ectopic Pregnancy.* Ectopic as well as intrauterine pregnancy may occur in contraceptive failures. However, in oral contraceptive failures, the ratio of ectopic to intrauterine pregnancies is higher than in women not using oral contraceptives since the drugs are more effective in preventing intrauterine rather than ectopic pregnancy. The higher ectopic-intrauterine ratio has been reported with both combination products and progestin-only oral contraceptives. 12) *Breast Feeding.* A small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs. The long-range effect to the nursing infant cannot be determined at this time.

Precautions: 1) A complete medical and family history should be taken prior to the initiation of oral contraceptives. Examination should include special reference to blood pressure, breasts, abdomen and pelvic organs, including Papanicolaou smear and relevant laboratory tests. As a general rule, oral contraceptives should not be prescribed for longer than 1 year without another physical examination being performed. 2) Under the influence of estrogen-progestogen preparations, preexisting uterine leiomyomata may increase in size. 3) Patients with a history of psychic depression should be carefully observed and the drug discontinued if depression recurs to a serious degree. 4) Because oral contraceptives may cause some degree of fluid retention, conditions which might be aggravated by fluid retention, such as convulsive disorders, migraine syndrome, cardiac or renal insufficiency or asthma require careful observation. 5) Patients with a past history of jaundice during pregnancy have an increased risk of recurrence of jaundice while receiving oral contraceptive therapy. If jaundice develops in any patient receiving such drugs, the medication should be discontinued. 6) Steroid hormones may be poorly metabolized in patients with impaired liver function and should be administered with caution in such patients. 7) Oral contraceptive users may have disturbances in normal tryptophan metabolism which may result in a relative pyridoxine deficiency. The clinical significance of this is yet to be determined. 8) Serum folate levels may be depressed by oral contraceptive therapy. This may complicate subsequent pregnancy with regard to folate deficiency. 9) The pathologist should be advised of oral contraceptive therapy when relevant specimens are submitted. 10) Certain endocrine and liver function tests and blood components may be affected by estrogen-containing oral contraceptives: a. Increased sulfobromophthalein retention. b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability. c. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T_4 by column, or T_4 by radioimmunoassay. Free T_3 resin uptake is decreased, reflecting the elevated TBG; free T_4 concentration is unaltered. d. Decreased pregnanediol excretion. e. Reduced response to metyrapone test.

Information for the Patient: Detailed Patient Labeling has been prepared for use by the patient and has been made available for distribution by the pharmacist.

Drug Interactions: Reduced efficacy and increased incidence of breakthrough bleeding have been associated with concomitant use of rifampin. A similar association has been suggested with barbiturates, phenylbutazone, phenytoin sodium and ampicillin.

Adverse Reactions: An increased risk of the following serious adverse reactions has been associated with the use of oral contraceptives (see **Warnings**): Thrombophlebitis; pulmonary embolism; coronary thrombosis; cerebral thrombosis; cerebral hemorrhage; hypertension; gall bladder disease; congenital anomalies. There is evidence of an association between the following conditions and the use of oral contraceptives, although additional confirmatory studies are needed: Mesenteric thrombosis; benign hepatomas; neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis. The following adverse reactions have been reported in patients receiving oral contraceptives and are believed to be drug related: Nausea and/or vomiting, usually the most common adverse reactions, occur in approximately 10% or less of patients during the first cycle (Other reactions, as a general rule, are seen much less frequently or only occasionally.); gastrointestinal symptoms (such as abdominal cramps and bloating); breakthrough bleeding; spotting; change in menstrual flow; dysmenorrhea; amenorrhea during and after treatment; temporary infertility after discontinuance of treatment; edema; chloasma or melasma which may persist; breast changes (tenderness, enlargement, and secretion); change in weight (increase or decrease); change in cervical erosion and cervical secretion; possible diminution in lactation when given immediately postpartum; cholestatic jaundice; migraine; increase in size of uterine leiomyomata; rash (allergic); mental depression; reduced tolerance to carbohydrates; vaginal candidiasis. The following adverse reactions have been reported in users of oral contraceptives, and the association has been neither confirmed nor refuted: Premenstrual-like syndrome; intolerance to contact lenses; change in corneal curvature (steepening); cataracts; changes in libido; chorea; changes in appetite; cystitis-like syndrome; headache; nervousness; dizziness; hirsutism; loss of scalp hair; erythema multiforme; erythema nodosum; hemorrhagic eruption; vaginitis; porphyria; impaired renal function.

Acute Overdosage: Serious ill effects have not been reported following acute ingestion of large doses of oral contraceptives by young children. Overdosage may cause nausea, and withdrawal bleeding may occur in females.

Mead Johnson PHARMACEUTICAL DIVISION

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Bilateral internal iliac artery ligation in cervical pregnancy: Conservation of reproductive function

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Like other forms of ectopic gestation, cervical pregnancy is a serious complication with potentially life-threatening consequences. Excessive bleeding almost invariably follows an attempt to evacuate this rare ectopic pregnancy. In most reported cases, hysterectomy has been required to control the severe hemorrhage. This paper reports for the first time the successful conservative management of cervical pregnancy in two patients by bilateral internal iliac artery ligation alone. Early recognition of the cervical pregnancy and prompt internal iliac artery ligation are stressed. (AM. J. OBSTET. GYNECOL. 134:145, 1979.)

CERVICAL PREGNANCY is a rare form of ectopic gestation in which implantation occurs in the cervical mucosa below the level of the internal os of the uterus. Like other forms of ectopic gestation, cervical pregnancy is a serious complication with potentially life-threatening consequences.

In 1953, Baptisti[1] said that most obstetricians would never see a cervical pregnancy and that those who did encounter the complication would wish they had not. This warning was occasioned by the severe bleeding that almost invariably attends either the spontaneous abortion or surgical evacuation of this pregnancy. In most reported cases, multiple transfusions and total abdominal hysterectomy have been required to control the hemorrhage. The resulting loss of childbearing function in a young patient with low parity is a central concern in the surgical management of cervical pregnancy.

This paper reports for the first time the successful conservative management of cervical pregnancy in two patients by bilateral internal iliac artery ligation alone. These cases demonstrate that in some patients the ligation of the internal iliac arteries may be an effective alternative to hysterectomy in the treatment of cervical pregnancy.

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Case reports

Case 1. C. B., a 17-year-old single woman, gravida 1, para 0, was admitted to the Gynecology Service at Loma Linda University Medical Center on January 3, 1970, after 3 weeks of cramping, lower abdominal pain, abnormal vaginal bleeding, and the presence of a pelvic mass. Her last menstrual period was November 28, 1969. The abdominal pain began with the onset of abnormal bleeding and progressively increased in intensity. Two weeks prior to this admission, an intravenous pyelogram and barium enema suggested the presence of a pelvic mass. A gynecologic consultation at that time confirmed a pelvic mass the size of a 12 week intrauterine pregnancy. However, a pregnancy test was negative. Sexual intercourse had occurred three months prior to hospitalization.

On admission, the patient's blood pressure was 120/76 mm Hg, pulse 100 bpm, and temperature 97° F. The findings of the general physical examination were normal. The abdominal examination revealed a readily palpable, firm, tender, suprapubic mass. There was no rebound tenderness. The cervix was closed, with some dark blood coming from the external os. A 10 to 12 cm soft, cystic, globular mass was found to be filling the pelvis. The cervix and uterus could not be readily distinguished from the mass, which projected into the posterior fornix of the vagina and appeared to displace the cervix anteriorly. The adnexa were not palpable. A urinary pregnancy test was negative and the urinalysis normal. The hemoglobin was 12.8 gms/100 ml and the white blood cell count was 14,200/cu mm with a slight shift to the left.

An exploratory laparotomy was performed on January 5, 1970, and showed the uterine corpus to be of normal size but elevated out of the pelvis by a 10 cm soft, cystic enlargement of the cervix. The tubes and

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Table I. Documented cases of cervical pregnancy and method of therapy in the English literature over the past 10 years (July, 1968, to July, 1978)

Group	Date of report	No. of cases	Treatment	
			Curettage, cervical packing, or suturing	Hysterectomy
Mortimer and Aitken[8]	1968	3	1	2
Strawn[9]	1968	1	1	0
Heller[7]	1968	1	0	1
Shinagawa and Nagayama[5]	1969	19	0	19
Jauchler and Baker[10]	1970	1	0	1
Fahmy et al.[11]	1971	1	0	1
Mitrani[12]	1973	1	0	1
Rothe and Birnbaum[13]	1973	3	0	3
Lange and Sjolie[14]	1975	1	0	1
Gabbe et al.[15]	1975	2	0	2
Whittle[16]	1976	1	1	0
Khosravi et al.[17]	1976	3	1	2
Ranade[18]	1978	1	0	1
Total		38	4 (10.5%)	34 (89.5%)

Table II. Summary of pertinent clinical findings in 38 cases of cervical pregnancy reported in the English literature, 1968 to 1978

No. of cases	38
Average age	30
(range)	(19-46)
Average gravidity	4.7
(range)	(1-11)
Average blood replacement*	6.4U
(range)	(0-14)
No. of cases with previous curettage	25 (65.7%)

*Based on 17 cases only. Not given in the 19 cases of Shinagawa and Nagayama and two other reports.

ovaries were normal. A diagnosis of cervical pregnancy was first considered at this time. The patient was placed in a low lithotomy position and redraped. Cautious exploration of the cervix with a uterine sound and with direct observation through the laparotomy incision revealed a marked dilatation and thinning of the cervical canal. The internal os was intact and the endometrial cavity was normal. Brisk, active bleeding was encountered during the exploration of the cervix. Because of the patient's age and parity, a bilateral internal iliac artery ligation was performed prior to any further attempt to evacuate the cervical pregnancy. The ligation was accomplished without difficulty. The cervix was then carefully curetted and a large amount of necrotic placental tissue and old clot was removed from the endocervical wall. Minimal bleeding was encountered during the evacuation, the total estimated blood loss during the procedure being 250 ml. No uterine packing was required and the patient's postoperative course was uneventful. The pathologic examination of the surgical curettings revealed portions of partially necrotic decidual tissue and chorionic villi.

The patient again became pregnant in February, 1973. The pregnancy terminated at 8 weeks with an incomplete, infected abortion. In September, 1974, total abdominal hysterectomy and bilateral salpingo-oophorectomy were required for chronic pelvic infection and recurrent bilateral tuboovarian abscesses.

Case 2. M. G., a 33-year-old married woman, gravida 3, para 2, abortions 0, was admitted to Loma Linda University Medical Center on March 16, 1971, with profuse vaginal bleeding at 11 weeks' gestation. Her last normal menstrual period was January 1, 1971. She had been seen in the outpatient clinic two weeks prior to admission, complaining of dark brown vaginal discharge. A pregnancy test was positive. A diagnosis of threatened abortion was made. On the day of admission, the patient was re-examined for heavier vaginal bleeding and cramping abdominal pain for the previous 9 days. The external os of the cervix was dilated 2 cm with a moderate amount of dark blood coming from the os. The uterus was enlarged, consistent with an 11 week pregnancy. A forceps was introduced through the dilated external os and an enlarged cystic cavity of the cervix was noted. Excessive vaginal bleeding followed immediately with a sudden loss of approximately 300 ml of blood. Intravenous fluids were started at once and the patient was taken directly from the outpatient clinic to the operating room for emergency surgery for a suspected cervical pregnancy.

Her past medical history revealed two previous cesarean sections, but there had been no previous gynecologic surgery. She had been treated for sarcoidosis in 1970.

On admission, the patient's blood pressure was 130/100 mm Hg, pulse 100 bpw, temperature 98.6° F. The preoperative hemoglobin was 11.6 gm/100 ml. The patient was given a general anesthetic agent, placed in a low lithotomy position, and prepared and draped for a combined vaginal and abdominal surgical approach. The cervical cavity and uterus sounded to 13 cm. The

Table III. A comparison of age, gravidity, and history of previous curettage in patients with cervical pregnancies from 1968 to 1978 and control subjects

	Report of Shinagawa and Nagoyama[5]		*Others*	
	Cervical pregnancy	*Control**	*Cervical pregnancy*	*Control†*
No. of cases	19	200	19	53
Average age	34	34	30	29
Gravidity	5.7	3.6	3.5	3.1
Previous curettage	13‡ (68%)	63 (32%)	12§ (63%)	18 (34%)

*Semirandom sampling of general clinic patients. Unmarried and sterile women were excluded.
†Random sampling of patients with incomplete abortion. Primigravid patients were excluded.
‡$P = 0.001$.
§$P < 0.05$.

internal os appeared intact and the endometrial cavity was normal. A 6 to 8 cm sacculation of the cervix was noted. An attempt to evacuate the pregnancy from the cervix resulted in further active, uncontrollable bleeding. At laparotomy, the cervix was approximately 8 cm in diameter, with a very thin cervical wall. On top of the cervix was a normal-sized uterine corpus. Because the patient desired to maintain her fertility, a bilateral internal iliac artery ligation was performed. The cervix was then thoroughly curetted. Moderate bleeding continued from the cervix but was well controlled with intracervical packing. The estimated total blood loss was 1,200 ml. The patient received 2 U of whole blood postoperatively. The pathology report revealed necrotic decidual tissue with chorionic villi consistent with cervical pregnancy.

Follow-up examinations revealed the resumption of regular, normal menstrual periods. A basal body temperature recording and endometrial biopsy confirmed ovulation. A hysterogram revealed a normal endocervical cavity and an intact internal os. The patient started oral contraceptive pills within 1 year following surgery and has continued to use contraception to the present time.

Comment

Cervical pregnancy is one of the rarest forms of ectopic gestation. Breen[2] reviewed 654 ectopic pregnancies encountered in 56,700 deliveries over a 20 year period. Only one cervical pregnancy (0.15%) was reported in this large series. Because cervical pregnancy is extremely rare, its reported incidence is highly variable. In 1966, Dees[3] recorded an incidence of one cervical pregnancy in 18,000 pregnancies. Sheldon and colleagues[4] reported a similar frequency of 1:16,000 over a 15 year period. On the other hand, Shinagawa and Nagayama[5] found a remarkably high incidence of one in 1,000 pregnancies in Japan.

Cervical pregnancies are infrequently reported in the literature. In 1961, Thomsen and Johansen[6] found only 80 recorded cases. In 1968, Heller[7] stated that approximately 120 cases had been described up to that time. Since 1968, 38 documented cases of cervical pregnancies have been reported in the English literature. These cases and their method of therapy are summarized in Table I.[7–19] Nineteen of the 38 case reports (50%) are from a single report from Japan. If these are excluded, there remain only 19 cases of cervical pregnancy in the English literature over the past 10 years. A summary of some pertinent clinical findings in these 38 cases of cervical pregnancy is presented in Table II.

The etiology of cervical pregnancy is unknown. Two factors appear to contribute to an ectopic cervical implantation: a previous surgical manipulation of the cervix (curettage) and a previous pregnancy. Shinagawa and Nagayama[5] attributed the apparent higher incidence of cervical pregnancy in Japan to the high frequency of therapeutic abortions in that country. They reported that 68% of 19 patients with cervical pregnancy had undergone an antecedent therapeutic abortion. In a control group of 200 women, a previous therapeutic abortion was found in only 32% (Table III).

In the remaining 19 cases of cervical pregnancies reported in the last 10 years, a history of a previous curettage was found in 63%. A control group of 53 patients admitted to Loma Linda University Medical Center for incomplete abortion was selected at random for comparison (Table III). All primigravid women were excluded. Eighteen (34%) of these patients had an antecedent curettage. This difference between the cervical pregnancy and control groups is statistically significant ($P < 0.05$).

A second possible etiologic factor is multigravidity. The large majority of patients have had several previous pregnancies. The average gravidity of the previous 38 patients with cervical pregnancy was 4.7. Only six cases of cervical pregnancy in patients in their first pregnancy have been reported.[17] One of the cases in

Table IV. The preoperative diagnosis in 38 cases of cervical pregnancies reported in the English literature from July, 1968, to July, 1978

Preoperative diagnosis	*No. of cases*	*Percentage*
Imminent, incomplete, or missed abortion	19	50
Cervical pregnancy	7	18
Septic abortion	2	5
Therapeutic abortion	2	5
Cervical neoplasm	2	5
Placenta previa	1	3
Intra-abdominal hemorrhage	1	3
Incompetent cervix	1	3
Not given	3	8
Total	38	100

this report is the seventh recorded instance of a cervical pregnancy in a primigravid patient.

The diagnosis of cervical pregnancy is infrequently made prior to surgery. The preoperative diagnoses of all cervical pregnancies reported in the last 10 years are listed in Table IV. The most frequent diagnosis was imminent or incomplete abortion. In only seven patients (18%) was a diagnosis of cervical pregnancy suspected prior to operative intervention. The wide variety of preoperative diagnoses indicates the frequently confusing clinical picture presented by these patients.

Early diagnosis of cervical pregnancy depends upon the obstetrician's constant awareness of its possibility and a very careful evaluation of the pelvic findings. Recently the diagnosis of cervical pregnancy by ultrasound has been reported.[19] The more frequent utilization of ultrasonography in the evaluation of vaginal bleeding in early pregnancy may increase the possibility of preoperative recognition of this complication.

In 1911, Rubin[20] set forth specific pathologic criteria as necessary to establish the diagnosis of cervical pregnancy: (1) the cervical glands must be opposite the placental attachment; (2) placental attachment to the cervix must be intimate; (3) the whole or a portion of the placenta must be situated below the entrance of the uterine vessels or below the peritoneal reflection of the anterior and posterior surfaces of the uterus; (4) fetal elements must not be present within the corpus uteri. Not all reported cases of cervical pregnancy have met these requirements because Rubin's criteria require pathologic examination of the excised uterus obtained either from surgery or from autopsy. Therefore, in 1959, Paalman and McElin[21] suggested several clinical objective signs to establish a diagnosis of cervical pregnancy: (1) a softened and disproportionately enlarged cervix equal to or larger than the corporal portion of the uterus, (2) products of conception entirely confined within and firmly attached to the endocervix, (3) a snug internal os, and (4) a partially open external os. The two cases presented in this report meet these criteria.

Approximately 90% of the reported cases of cervical pregnancy during the past 10 years have required total abdominal hysterectomy to control excessive bleeding (Table I). A conservative management of cervical pregnancy by curettage, cervical packing, ligation of the cervical arteries, and suturing of the cervix has been successful in only a small number of patients. The majority of the conservatively managed cases have been in pregnancies of less than 8 weeks. When the pregnancy has progressed beyond 8 weeks, major bleeding is usually encountered and hysterectomy is necessary.

In 1965, Dodeck[22] suggested the consideration of bilateral ligation of the internal iliac arteries along with a transabdominal cervicotomy as a conservative approach to the advanced cervical pregnancy. However, he did not have any experience with this approach. Internal iliac artery ligation has been reported in conjunction with abdominal hysterectomy in several cases of cervical pregnancy in which severe bleeding and unusual complications existed.[4, 17] The only previous report of an attempt to perform internal iliac artery ligation for hemostasis was by Shinagawa and Nagayama.[5] In reporting their 19 cases of cervical pregnancy, they stated that they were unable to obtain satisfactory hemostasis by ligation of the internal iliac arteries. However, they did not list the number of cases in which internal iliac artery ligation was attempted or describe the circumstances surrounding the failures.

Internal iliac artery ligation is rarely performed by obstetricians and gynecologists. In 1973, Sack[23] reported that 94% of obstetrics and gynecology specialists he surveyed in Southern California had not performed the procedure in a 10 year period. He found that most ligations were performed in large teaching centers. However, he stressed that all pelvic surgeons should maintain their proficiency in this procedure by occasionally exposing and identifying the internal iliac arteries during the course of other pelvic surgery. Demonstration of the technique, if not the actual ligation of the arteries, should be an integral part of every residency training program.

Pregnancy following bilateral internal iliac artery ligation is well documented.[24] The subsequent pregnancies have been normal with normal deliveries, and there has been no increased incidence of obstetric complications. The prognosis for future pregnancies following the conservative management of a cervical gestation is unknown because of insufficient experience to determine the likelihood of complications in subsequent pregnancies. However, normal pregnancies and vaginal deliveries after a previous cervical

pregnancy have been reported.[1, 4] Cervical incompetence would be unexpected unless the internal os was compromised during surgery. The risk of a subsequent cervical pregnancy is unknown.

This report documents for the first time the successful management of a cervical pregnancy by bilateral internal iliac artery ligation. Conservation of reproductive function was achieved. In addition, the amount of blood loss in these two patients was considerably less than has been reported in the literature in similar circumstances. Furthermore, by this approach, the evacuation of the products of conception can be safely and thoroughly accomplished through the vagina.

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Discussion

Dr. Frank LeCocq, Jr., Yakima, Washington. In this age of advanced medical knowledge and technology, a "first time" report is rare, yet Dr. Nelson has described and for the first time successfully utilized a surgical technique in the treatment of a catastrophic obstetric complication. Being a longtime champion of the use of internal iliac artery ligation, I am privileged to discuss and confirm this accomplishment. As has been stated, various authors have suggested but did not utilize the technique. Finally internal iliac artery ligation was performed in cervical pregnancy, but in conjunction with total abdominal hysterectomy. In reviewing all of the available literature, I can confirm that Dr. Nelson may take credit for the first successful use of internal iliac artery ligation in the preservation of child-bearing function in cervical pregnancy.

This rare nidation and development of an ectopic pregnancy in the cervix presents overwhelming problems in diagnosis and management. Any discussion of this interesting lesion could include Studdiford's[1] classic publication on this subject in 1945. He discussed 28 cases, including Tarnier's fatal case of cervical pregnancy in 1887 resulting in the delivery of a viable term infant. Also described was Connor's unique case of cervical pregnancy occurring in a cervical stump following a previous supracervical hysterectomy. Aside from these medical oddities, Dr. Nelson has adequately brought us to the present, referable to the clinical aspects of this most infrequent but important lesion.

The pathophysiology of the hemorrhage is based upon nidation of the ovum in a most vascular area of the uterus, which unfortunately consists of only 15% musculature with contractile potential. The rarity of the condition in itsself leads the unsuspecting clinician into the "valley of the shadow," not anticipating the horrendous bleeding that will follow attempts at its removal. Dr. Nelson noted that only 18% of all reported cases were considered as cervical pregnancy prior to surgery. Though extremely rare, this condition must be considered by the clinician to avoid catastrophic and even fatal hemorrhage. In the past, only 10% of cervical pregnancies have been treated with less than hysterectomy, and these invariably were within the early

weeks of gestation. Used were various techniques of curettage, packing, and suture.

Maintenance of child-bearing function following internal iliac artery ligation has been a fascinating chapter in the evolution of this surgical procedure. The unique, efficient collateral blood supply of the pelvis, so well described by Burchell,[2] must be reconsidered. Mengert and Burchell[3] have accumulated five cases in which pregnancy has occurred following internal iliac artery ligation; moreover, in three cases bilateral ovarian artery ligation was performed as well. In a recent report from Mexico,[4] 90 cases of internal iliac artery ligation were described, of which the uteri were retained in 22 cases. Of these, seven patients subsequently became pregnant. In a recent personal communication from Burchell,[5] the use of absorbable suture material in the ligation is suggested. This will enhance recanalization of the ligated vessels and thus aid in preserving fertility.

In discussing the etiology of cervical pregnancy, previous surgical trauma, older age, multiparity, abortion, leiomyomas, uterine atrophy, malformations, and even oral contraceptives have been considered by various authors as contributing factors. Certainly the Japanese observation that over 60% of their cases of cervical pregnancy were preceded by therapeutic abortion is indisputable. I would question Dr. Nelson's use of 53 random clinic patients as controls to support this conclusion.

In that Dr. Nelson's publication gives us still another indication for internal iliac artery ligation, I would again like to advocate the teaching of the technique to all operating gynecologists. Although rarely necessary, its use can be lifesaving. I recall, with some amusement, a "Letter to the Editors" of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY following our last discussion of this topic in 1973. Dr. Buschbaum,[6] of Chicago, commenting on our meeting, indignantly wrote, "Operating in the pelvis without the ability to do a hypogastric artery ligation is similar to teaching an electrician intricate wiring circuits without first teaching him to turn off the current."

I wish to thank Dr. Nelson for his prompt submission of this document and congratulate him on this exciting contribution to the medical literature. In that the duration of pregnancy is vital in the treatment and prognosis, I will conclude with a question regarding his Case No. 1: Does he speculate the duration of this pregnancy was 3 weeks as indicated by the menstrual history or possibly 12 weeks as indicated by the clinical findings or the social history?

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DR. RICHARD N. BOLTON, Portland, Oregon. I would like to ask Dr. Nelson if he has had any experience, or knows of anyone else who has had any experience, using a high cervical cerclage type of procedure for this form of bleeding—something like you would use for an insufficient cervix.

DR. NELSON (Closing). There is one report in the European literature of an approach similar to a cerclage type of procedure. They actually clamped and ligated the cervical branch of the uterine artery, as done in performing a vaginal hysterectomy, and were successful in controlling the bleeding.

In answer to the question about the duration of pregnancy in Case No. 1, I would have assumed by the size of the cervical enlargement, despite the recent menstrual period within three weeks, that the pregnancy was further advanced than stated. According to our biostatistician, there were sufficient numbers in the study for the control group to pass a chi-square test for validity of the analysis.

In reviewing the past published reports, a rather common theme seemed to develop—late first-trimester or early midtrimester bleeding, a diagnosis of incomplete abortion, and attempted evacuation of the pregnancy with resulting uncontrollable hemorrhage and hysterectomy. One does not undertake bilateral internal iliac artery ligation without considerable concern. However, when one considers the alternatives for these patients, it seems an appropriate choice in selected patients.

Vasa previa

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An active obstetric service can expect to have one perinatal death each year due to vasa previa. Unfortunately, little has been done to improve the diagnosis and treatment of this condition, which presents no risk to the mother but is often fatal to the fetus. The various clinical pictures which can be associated with vasa previa are presented, along with a discussion of the techniques readily available for making the diagnosis: palpation and visualization, amnioscopy, fetal heart monitoring, and various tests for the presence of fetal hemoglobin. (AM. J. OBSTET. GYNECOL. 134:151, 1979.)

THE PAST DECADES have seen the development of a wide array of chemical, physical, and electronic techniques designed to detect even subtle changes in the fetal environment and threats to fetal well-being. Yet vasa previa, with one of the highest fetal mortality rates of any obstetric condition, continues to receive scant attention. Indeed most obstetricians look upon its diagnosis and management with utter despair, lack any familiarity with the various clinical features of the condition, and consistently fail to utilize the techniques which are available for establishing the diagnosis.

Although vasa previa is certainly not common, Driscoll[1] reported one death per year from vasa previa at the Boston Lying-In Hospital. The incidence of vasa previa is in the range of one for each two thousand to three thousand deliveries,[2, 3] and it is quite possible that with increased knowledge of the problem the true incidence is even higher. Thus a moderately active obstetric service can expect one case each year.

It is the purpose of this paper to present a case report followed by a discussion of the diagnosis and treatment of vasa previa, in the hope that with awareness of this problem fetal survival will increase.

Case report

The patient was a 26-year-old woman, gravida 3, para 2, with an uneventful prenatal course, admitted to the hospital at 41 weeks' gestation. The membranes had ruptured spontaneously 1 hour earlier. At the time of admission, a sheet of the membranes, approximately 15 cm in length, was extending out from the vaginal introitus, lying up against the patient's right thigh. This was lifted up—and possibly some slight traction exerted—by the aide shaving the vulvar area. This handling of the sheet of membranes was followed by a gush of bright red blood.

Fetal movements were no longer felt by the patient and fetal heart tones could no longer be heard. During labor, which was augmented with oxytocin, the severed end of the umbilical cord prolapsed through the vagina, making the diagnosis obvious. After 3½ hours of labor the patient was delivered of a 7 pound, 14½ ounce stillborn male infant. The placenta was delivered and demonstrated a velamentous insertion of the umbilical vessels with rupture.

Clinical features

Most obstetricians, when they think of vasa previa, picture the same sequence of events that occurred in this case: spontaneous rupture of the membranes, laceration of the umbilical vessels, fetal hemorrhage, and subsequent fetal death. However, this is by no means the universal picture. Previous authors[4–6] have clearly demonstrated that many, sometimes the majority, of cases of vasa previa are of such a nature as to permit the diagnosis to be made and treatment to be instituted. A high index of suspicion is important in making the diagnosis and this requires a familiarity with the various clinical features associated with vasa previa:

1. Bleeding need not be present. Vasa previa is defined as an anomaly of the insertion of the umbilical cord into the placenta in which the umbilical vessels traverse the lower uterine segment and present in advance of the fetal presenting part. Thus, even if there is no rupture of the blood vessels, these may be compressed against the bony pelvis by the fetal head, resulting in hypoxia and possible fetal death. Whereas vasa previa with bleeding is associated with fetal death in 75% to 100% of cases, fetal death secondary to cord

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compression has a reported incidence of 50% to 60%.[7, 8]

2. The vessels do not have to traverse the os. This anatomy does not fit precisely into the definition of vasa previa, but the clinical picture, diagnosis, and treatment of the patient are the same as in vasa previa. Torrey[9] has classified this occurrence as a separate group, which he called "abruptio of the umbilical vessels." The mechanism involved is a tear in the amniotic sac which extends into the velamentous vessels.

3. The membranes need not be ruptured. A velamentous insertion of the cord is a prerequisite for vasa previa. As such, the vessels are no longer protected by Wharton's jelly and are particularly vulnerable to rupture. Thus in a significant number of cases of vasa previa the vessels are torn prior to the rupture of the membranes. This occurred in four of the seven cases of vasa previa reported by Vago and Caspi.[2] Bleeding from lacerated umbilical vessels, with the membranes intact, has also been reported by Mitchell and associates,[5] Vogt,[10] and Benirschke.[11] Vasa previa should also be considered in the differential diagnosis of third-trimester bleeding. Cases where the bleeding has ceased spontaneously and recurred during the seventh and eighth months of pregnancy have been reported.[2] It is postulated that the bleeding ceased because of thrombus formation and recurred secondary to vessel trauma at the time of delivery. In none of the reported cases, however, were the episodes of antepartum bleeding definitely proved to be fetal in origin. Tests to demonstrate the presence of fetal blood should be performed in all cases of antepartum bleeding. This will help clarify the role of vasa previa as a cause of third-trimester bleeding.

4. Bleeding can begin long after the membranes have ruptured. In these cases the initial tear in the membranes does not involve the velamentous vessels. With the onset of labor and cervical dilatation the tear can then extend to involve the vessels.[12]

Diagnosis

Vasa previa is associated with one of the highest fetal mortality rates of any of the complications of pregnancy. Early diagnosis and treatment are essential if this high rate is to be lowered. The most important factor in making the diagnosis is to maintain a high index of suspicion. As can be seen from the varied clinical picture, the diagnosis has to be considered not only in all cases of antepartum and intrapartum bleeding but also in cases of fetal distress in the absence of bleeding. Small amounts of bleeding should not be dismissed. Variations in fetal heart rate need to be evaluated. The combination of scant vaginal bleeding and fetal distress is strongly suggestive of vasa previa.

Several modalities are available to aid in establishing the diagnosis: (1) direct visualization and palpation of the vessels, (2) fetal heart rate monitoring, (3) amnioscopy, and (4) tests for the presence of fetal blood components.

Visualization and palpation of the vessels were reported over a century ago. The difficulty is in distinguishing the velamentous vessels from a presenting umbilical cord. The vessels can be identified by their smaller diameter, lack of mobility, and the absence of a free space around them. Curl and Johnson[13] palpated the artery and demonstrated that pressure on the vessel resulted in bradycardia within 30 seconds. The fetal heart rate returned to normal when the pressure was released. Fetal bradycardia was again noted after abdominal pressure had been exerted to force the vertex into the pelvis. The fetal electrocardiogram is invaluable in assessing the heart rate variability associated with vasa previa.

Barham[8] has advocated rupturing the membranes under direct vision, a procedure he calls "amnioscopic amniotomy." His admonition to "encourage more obstetricians to have a good look at surgical induction of labor, preferably with the amnioscope"[14] is of special interest to this case. The patient was 1 week past term and had been scheduled for admission to the hospital at 7:00 AM that day for elective induction of labor. She was admitted at 6:30 AM, with a history of spontaneous rupture of the membranes an hour earlier. This circumstance relieved her obstetrician of unknowingly contributing to the death of the baby by his elective interference. Amnioscopy should certainly be considered in the evaluation of a patient presenting with antepartum hemorrhage and/or fetal heart rate irregularity or bradycardia.[8] If the patient is bleeding, amnioscopy makes it easier to collect blood for examination and testing.

Since vasa previa involves the loss of fetal and not maternal blood, detection of the constituents of fetal blood is the key in establishing the diagnosis. As far back as 1912, Williamson recommended examination of the blood for normoblasts and nucleated red blood cells. He later abandoned the idea as impractical, since most deliveries were being performed at home. However, a stained blood smear still remains as an extremely valuable tool in the diagnosis of vasa previa. The diagnosis can also be established by demonstrating the presence of fetal hemoglobin. Over the years various tests have been developed, including the use of spectrophotometry, but use of the Apt test, as proposed by Israel[15] in 1961, offers a method which is simple to perform, does not require sophisticated equipment, and provides the results in a few minutes.

In this test 2 to 3 ml of the bloody fluid are mixed with an equal amount of water and centrifuged (2 minutes at 2,000 rpm), and the supernatant is decanted. One part of 0.25N (1%) sodium hydroxide is then mixed with five parts of the decanted pink fluid. Within 2 minutes adult hemoglobin will form an alkaline-hematin compound, resulting in a yellow-brown color. Fetal hemoglobin is alkali resistant, and, in this case, the solution will remain pink. The test may yield a false negative result if the original blood sample contained very little hemoglobin. Sickle cell anemia and thalassemia may give misleading results, since appreciable amounts of fetal hemoglobin are present in the maternal blood in these diseases. A simpler technique for the detection of fetal hemoglobin was described by Ogita[16] in 1976. It can be performed in a few minutes using only chemical reagents. No centrifuge or other equipment is needed. The test can be easily and rapidly performed in the obstetric suite. One drop of the fresh heparinized blood sample is added to five drops of the alkali (0.1N potassium hydroxide) and shaken for 2 minutes. Ten drops of a precipitating solution (400 ml of 50% saturated ammonium sulfate and 1 ml of 10N hydrochloric acid) are added. The mixture is dropped on filter paper with a capillary tube to make a ring approximately 20 mm in diameter. Denatured adult hemoglobin and cell debris will remain at the center. Alkali-resistant fetal hemoglobin will form a colored ring at the periphery.

Treatment

Few situations in obstetrics so dramatically illustrate the need for a correct diagnosis before instituting treatment. Vasa previa is frequently misdiagnosed as abruptio placentae or placenta previa. The management of these conditions generally includes artificial rupture of the membranes, a maneuver which is usually catastrophic in the case of vasa previa.

The treatment of vasa previa is undertaken solely for the fetus. Vasa previa is unique in that it is the only condition in which there is a high fetal mortality rate in the absence of maternal mortality. Treatment is predicated on the fact that the infant, having a total blood volume of approximately 250 cc at term, cannot really tolerate the loss of blood. Immediate delivery is mandatory if the fetus is alive and is to be rescued. If the cervix is fully dilated and vaginal delivery can be accomplished rapidly, this is the method of choice. More often cesarean section is required. Transfusion of the baby may be necessary following delivery, and a pediatrician should be present for the delivery.

A high index of suspicion, familiarity with the clinical features, and utilization of the readily available diagnostic tests are needed if we are to prevent needless deaths from this tragic accident of pregnancy.

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Discussion

Dr. William J. Spanos, San Bernardino, California. With a case report of a stillborn term infant Dr. Pent has brought to our attention and consideration a problem neglected on most obstetric services. The problem is not neglected because of lack of concern but because of infrequency of the problem, difficulty in diagnosis, and shortness of time to save the involved infant even if the diagnosis is suspected. The problem is indeed formidable when one considers the instances of vaginal bleeding that occur during labor either as bloody show on entry to the labor room or during the active phase secondary to stretch or minute lacerations of the cervix.

Vasa previa was first described in 1773, yet in over 200 years there are less than 200 cases reported in the literature. We are told that velamentous insertions are not uncommon, ranging from an estimated 1% in normal uncomplicated gestations to approximately 10% in multiple pregnancies.[1] Also in one large series vasa previa was encountered in one of every 2,761 deliveries.[2] If these statistics are accurate, why is vasa previa not recorded more often in the literature? One reason is that a number of cases are undiagnosed. In some cases the diagnosis is not made until after the fetal loss and it has been suggested that few physicians are tempted to report undiagnosed failure.

Each of the papers on this subject in the literature seems to offer a slightly different definition of vasa previa. Dr. Pent gives us a concise, inclusive definition, stating that vasa previa is an anomaly of the umbilical cord insertion in which the umbilical vessels traverse the lower uterine segment presenting in advance of the fetus. With this definition it becomes obvious that bleeding need not be present for the fetus to be at risk as the presenting part may compress the vessels against the pelvic wall and thus cause hypoxia and possible fetal death. Present-day practice of fetal monitoring should alert the obstetrician to hypoxia and thus increase salvage when the problem is only compression of the vasa previa vessels. More important we are reminded by Dr. Pent that the needed tools to make the diagnosis of ruptured fetal vessels and potential rapid fetal death in vasa previa have been available to us for years. The Apt test to distinguish between adult and fetal hemoglobin was described 25 years ago and proposed for use in this problem in 1961 by Israel.[3] Today Dr. Pent has brought to our attention an even more simple test for fetal hemoglobin as proposed by Ogita in 1976. The question now is will we as practicing obstetricians remember this only as an interesting case report or will we insist that our obstetric services have available the chemicals needed and that each bleeding episode be checked for fetal hemoglobin? The reward will be infrequent but very satisfying if an infant that otherwise would have been another stillbirth statistic is saved because of this effort.

Dr. Pent has reported a case in which his results were not as he would have liked but by so doing he brings to our attention a subject that in most obstetric textbooks receives at most two paragraphs but to date has a fetal mortality rate varying from 75% to 100%.

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Dr. E. Forrest Boyd, Jr., Los Angeles, California. This is an excellent step in our progress in salvaging fetal lives although it possibly opens a little bit of door temporarily for medical-legal action because, as this becomes known, obviously and more people are going to say, "Well why didn't you save my baby?" even though this is a very rare occurrence. The advent of ultrasound, particularly real-time ultrasound, introduces a possible additional aid, and I wonder if Dr. Pent would want to comment on this use of real-time sonography and possibly following the vessels to their origin. I am personally not that adept at it yet. We have not had it very long, but it is possible to spot the vessels implanted low in the uterus. I think another important facet is to document the actual placenta. How many of us, over the years, have commented, "Well this was a velamentous insertion," and thrown the placenta away. Maybe the pregnancy was not perfectly alright and there might have been something that we did not know about. So I think this might be something to which we can alert our house staff. Needless to say, the value of fetal monitoring and testing for fetal blood is obvious. We spend thousands of dollars looking for babies with phenylketonuria and hypothyroidism and this type of rarity, and yet how much would this cost just to routinely check all bleeding for fetal blood prior to delivery? This might be very valuable. A brief review of our records revealed three cases I shall mention. We examined a 20-year-old primagravid woman at 41½ weeks. The monitors showed severe bradycardia, and a cesarean section was done immediately without any further diagnostic procedures. A 7 pound, 5 ounce baby with Apgar scores of 4 and 6 was delivered, and a low-lying, posterior, velamentous placenta was noted. Another patient, a 30-year-old woman, gravida 4, para 3, at 40 weeks underwent spontaneous vaginal delivery of an 8 pound baby with Apgar scores of 8 and 8; a battledore placenta with a very thin, long portion of it low in the uterus was noted. On the other side of the coin, a third patient, 34 years of age, para 2, was admitted at 36 weeks. She had had decreased fetal movements for 2 days. A nonstress test was performed and showed bradycardia which was timed for 37 minutes. Thirty-seven minutes from the time this was first noted, the baby was delivered by cesarean section. The infant weighed 4 pounds, 14 ounces, and the placenta with velamentous insertion was implanted anteriorly and high in the fundus. The baby died.

This report raised our awareness of a heretofore seemingly unavoidable, but now increasingly preventable tragedy.

Dr. William H. Hindle, Honolulu, Hawaii. I reviewed the experience of Kapiolani Hospital, in Honolulu. Under the I.C.D.A. Code, vasa previa is coded under 663.5, which is velamentous insertion of the umbilical cord. Vasa previa is a subcode of that. I reviewed the delivery records of the last 5 years, 1973 to 1977. During that time there were 26,375 term births at Kapiolani Hospital. I was able to document 22 cases of confirmed velamentous insertion of the umbilical cord. This is a ratio of one case to every 1,199 term deliveries during that time. Of interest in reviewing these 22 cases was the number of additional major obstetric complications in association with velamentous insertion of the cord. There were two sets of twins, two breech presentations, four premature infants (by weight), four cases of fetal distress, one prolapsed cord, one fetus with multiple congenital anomalies, one persistent posterior presentation with mid-forceps delivery, one transverse arrest with delivery by mid-forceps rotation, and one bona fide vasa previa with fetal death. Thus, 17 of the 22 cases (or 77%) had an additional diagnosis of a major obstetric complication. The one case of vasa previa was in a 29-year-old, white woman,

gravida 3, para 2, abortions 0, with an expected date of confinement of August 9, 1973, who was admitted on August 1, 1973. She gave a past history of a 1 hour labor with the previous delivery. She lived more than a half hour's driving time away from the hospital. She and her husband desired Lamaze labor and delivery. After discussion with the couple, they requested elective induction of labor. During her prenatal course, she had a urinary tract infection. During the first trimester, she had an episode of vaginal bleeding with a gush of bright red blood which responded to conservative management with no recurrence of the bleeding. For four months prior to admission, she had had strong Braxton-Hicks contractions. She was very apprehensive about her previous short labor. She had been told by her previous obstetrician, after vaginal examination the day before she was delivered in her previous pregnancy, that the cervix was closed, long, and thick, and that it would probably be at least a week before delivery. This added to her apprehension. On admission the cervix was 3 cm dilated, 75% effaced, and soft with the vertex at the 0 station. The membranes were stripped and were clear to palpation. Amniotomy was followed by a large gush of dark red blood which persisted. Efforts to tamponade the fetal head against the lower uterine segment were carried out. The fetal heart tones became irregular. She developed active uterine contractions. The clinical diagnosis was probable vasa previa. She was delivered by emergency cesarean section, unfortunately of a stillborn infant. Gross inspection and subsequent pathologic examination revealed a long, velamentous insertion of the cord, with rupture of a velamentous vessel associated with hemorrhage and a pale stillborn fetus. Of further interest was the umbilical cord which had an anomaly, only two vessels. Thus, of the confirmed coded diagnoses of velamentous insertion of the umbilical cord at Kapiolani Hospital, 77% had additional major obstetric complications. I wonder if, in his review of the literature, Dr. Pent found note of this apparent association.

DR. LOUIS BARTOLUCCI, San Francisco, California. By no means intending to answer the question asked of Dr. Pent, I would like to comment on the fact that ultrasound, although not able to show directly "vasa previa," should routinely demonstrate the placental implantation and its limits so that the confusing entity of placenta previa, partial or total, be eliminated. I think that every time painless third-trimester or intrapartum bleeding is presented, an ultrasound scan should either introduce or reinforce the suspicion of "vasa previa."

DR. PENT (Closing). I have had no personal experience with the Ogita test, having discontinued the practice of obstetrics long before he described his test. However, I am firmly convinced that it can be performed by any trained paramedical personnel. In one of my lighter moments, this summer, I considered having a slide showing a very sophisticated piece of equipment, with lots of dials, lights, and buzzers, which would be marketed for $5,000 or $10,000. Then every hospital delivery unit would have one. Behind the unit I was going to have a chimpanzee, sitting there with the two reagents, performing the test.

Dr. Bartolucci has answered Dr. Boyd's question relating to ultrasound. Although the umbilical artery and veins have been distinguished by ultrasound as they course through the umbilical cord, I believe that there would be difficulty in identifying the vessels deep down in the bony pelvis.

In reply to Dr. Hindle, velamentous insertion is associated, in a significant percentage of cases, with the absence of one umbilical artery and with a higher incidence of congenital anomalies. The baby in this case report was found to have a horseshoe kidney at autopsy.

Pregnancy complicated by diabetes mellitus in private practice: A review of ten years

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Portland, Oregon

Two hundred private diabetic patients delivered of their infants (202) in a private hospital were evaluated for a 10 year study period (1968 to 1977). There were no maternal deaths. An 88% overall survival rate of viable infants compared favorably with that of other reported series. Analysis of each of the 10 years demonstrated marked changes in management and consequent changes in fetal survival, morbidity, and mortality rates. No neonatal deaths occurred during the last 3 years of the study period and the mortality rate in viable infants was 6.8%. There has been no significant temporal change in the incidence of toxemia or hydramnios. Fifteen stillbirths and ten neonatal deaths were analyzed to identify significant factors or parameters. Attention is directed to sex ratios (male:female) of 3:1 for stillbirths and 3:2 for infants affected with respiratory distress syndrome. Conservative use of accessory testing and antepartum hospitalization was obvious. The question of the necessity for expensive and intensive regimented institutional management is addressed. A minimum management regimen is proposed to be used in conjunction with the private obstetrician's clinical judgment and expertise. (AM. J. OBSTET. GYNECOL. 134:156, 1979.)

THE PAST TEN YEARS encompass major advancements in assessment of fetal pulmonary maturity and fetoplacental well-being. Though these tests are not without their vagaries of interpretation, they have significantly affected management of the diabetic pregnancy. It is the purpose of this study to evaluate the management and outcome of pregnancies complicated by diabetes mellitus in private practice during a 10 year period.

Material and methods

The patients included all pregnancies of 20 weeks' gestational age or greater complicated by diabetes mellitus, delivered at Good Samaritan Hospital and Medical Center, Portland, during the years 1968 through 1977. The 18 bed Diabetic Unit of the hospital is unique in this area, offering classes in self-management and affording a less expensive alternative to hospitalization for diabetic control. We are fortunate to have a group of diabetologists, located near the hospital, who have been instrumental in the development of this unit and who have provided diabetic care for 85% of the patients in this study, exclusive of Class A patients. Many different Board-certified or Board-qualified obstetricians rendered care. A variety of pediatricians were involved in care of the newborn infant; however, one pediatric group accounted for 76% of this care.

From the Good Samaritan Hospital and Medical Center.

Presented by invitation at the Forty-fifth Annual Meeting of the Pacific Coast Obstetrical and Gynecological Society, Gleneden Beach, Oregon, September 26-30, 1978.

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Results

During the period January 1, 1968, through December 31, 1977, there were 19,673 deliveries at Good Samaritan Hospital and Medical Center. Two hundred of these pregnancies were complicated by diabetes, for an incidence of 1.02%. Of those recorded, 97 infants were male and 93 were female. Significant congenital anomalies occurred in nine infants (4.5%). The average maternal age was 25.8 years with a range from 15 to 39 years. The averages of gravidity and parity were 2.35 and 0.96, respectively. There were 54 (28.4%) primagravid women. No significant year-to-year difference was noted for maternal age, gravidity, or parity.

Table I classifies the material according to the criteria of White and associates.[1]

One hundred thirty-eight pregnancies (69%) were delivered by cesarean section. Excluding Class A patients, 117 (79.6%) were delivered by cesarean section. Table II compares delivery modality of the study group with all deliveries during the same period. Diabetic indications dictated primary cesarean section in 63 patients (31.5%). Primary cesarean sections were performed in 21 cases (10.5%) for other indications.

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Table I. Case material by year and class

Year	White's classification						Total
	A	B	C	D	F	R	
1968	3	3	9	3			18
1969	2	6	7	3			18
1970	3	4	15	1			23
1971	6	1	15	0			22
1972	4	1	8	2			15
1973	4	3	9	2			18
1974	4	1	5	3			13
1975	6	0	7	1			14
1976	13	3	16	3	2		37
1977	8	1	10	3			22
Total	53	23	101	21	2		200

Table II. Mode of delivery of study patients compared to general hospital population

Mode	Study patients		All patients	
	No.	%	No.	%
Primary cesarean sections:	84	42.0	1,687	8.6
Diabetic indications	63	31.5		
Other indications	21	10.5		
Repeat cesarean sections	54	27.0	447	4.8
Total cesarean sections	138	69.0	2,634	13.4

Table III. Fetal outcome related to classification of White

Class	Total	Stillborn	Neonatal deaths	Perinatal mortality rate (%)
A	54	2	1	5.5
B	23	2		8.7
C	102	8	7	14.7
D	21	3	2	23.8
F	2			
R				
Total	202	15	10	12.4

Table IV. Fetal outcome by year

Year	Stillborn		Neonatal deaths		Perinatal deaths	
	No.	%	No.	%	No.	%
1968	1	5.3	2	10.5	3	15.8
1969	2	11.1	1	5.5	3	16.7
1970	2	8.7	5	21.7	7	30.4
1971			1	4.5	1	4.5
1972	3	20.0			3	20.0
1973			1	5.9	1	5.9
1974	2	15.4			2	15.4
1975	1	7.1			1	7.1
1976	2	5.4			2	5.4
1977	2	9.1			2	9.1

Repeat cesarean sections were performed in 54 patients (27%). There was no significant change in rates from year to year.

Complications of pregnancy included toxemia in 33 patients, hydramnios in 32 patients, premature rupture of the membranes in 13 patients, and premature labor with intact membranes in 15 patients. Analysis of cases with these complications did not demonstrate any year-to-year change.

The overall survival rate of viable (28 weeks or greater) infants was 88.1%. One stillborn infant in 1969 at 24 weeks' gestation was the only infant in the study born at less than 28 weeks. Table III relates White's classification to fetal loss. The overall perinatal mortality rate was 12.4%. Considering only Class B through R pregnancies the perinatal mortality rate was 14.8%. Table IV relates fetal loss to year. A definite decrease in neonatal mortality rate is noted with no neonatal deaths occurring during the last 4 years.

Stillbirths. The results of an in-depth analysis of the 15 stillborn infants are presented in Table V. The sex ratio of male to female infants is 3:1; however, this difference is not statistically significant. Toxemia was present in almost half of the cases. All patients with hydramnios also demonstrated toxemia. The three infants listed as having evidence of pulmonary maturity had lecithin-sphingomyelin ratios of 4:1, 2.5:1, and 2.8:1, respectively. The time intervals from amniocentesis to fetal death were 6 days, 4 days, and 1 day, respectively. One of the two congenital anomalies was severe anencephaly. The other was diagnosed at autopsy as stillbirth secondary to true knot in the cord.

Neonatal death. Table VI summarizes an in-depth analysis of the 10 neonatal deaths. All infants died of hyaline membrane disease diagnosed either at autopsy or by clinical course of respiratory distress. Two cases admitted in advanced premature labor were delivered vaginally. Premature labor dictated delivery time in three cases. Delivery of the remaining seven cases, occurring prior to 1972, was timed empirically based on past obstetric history and clinical evaluation, including hydramnios in four cases and toxemia in one case. Fetography performed in two cases did not demonstrate distal femoral epiphyses. No other tests of fetal well-being or fetal maturity were reported.

Respiratory distress syndrome (RDS). The incidence of RDS from year to year fluctuates markedly between 10% and 43% but does not demonstrate any statistically significant change. The severity of distress has decreased, resulting in no neonatal deaths since 1973. The sex ratio of affected infants was 3 male to 2 female. Of 52 infants, 31 were male and 19 were fe-

Table V. Analysis of 15 stillborn infants

Sex:	
Male	9
Female	3
Gestational age (wk.)	
Average	34.2
Range	24-37
Birth weight:	
Average	5 pounds, 14 ounces
Range	3 pounds, 7 ounces to 9 pounds
Toxemia	7 (47%)
Hydramnios	3 (20%)
Coexistent toxemia and hydramnios	3 (20%)
Results of tests for fetal maturity:	
None	8
Immature	4
Mature	3
White's classification:	
A	2
B	2
C	8
D	3
Congenital anomalies causing death	2

Table VI. Analysis of 10 neonatal deaths

Sex:	
Male	4
Female	6
Gestational age (wk.):	
Average	34.2
Range	32-37
Birth weight:	
Average	5 pounds, 6 ounces
Range	3 pounds, 8 ounces to 8 pounds, 10 ounces
White's classification:	
A	1
C	7
D	2

Table VII. Average number of days in hospital

	All Classes	*Classes B to R*
Maternal:		
For delivery	6.1	6.8
Including antepartum admissions	7.2	8.3
Neonatal:		
At Good Samaritan	6.8	7.6
Including transfers to University of Oregon Medical Center	7.3	8.3

male, and in two cases sex was not recorded. These deviations are not statistically significant. Amniocentesis for fetal pulmonary maturation was utilized in 10 of the 52 pregnancies. X-ray films to determine fetal age were obtained in 13 cases. In 29 pregnancies, no tests for fetal maturity were performed. Delivery was effected because of premature labor in nine cases and premature rupture of the membranes in six cases.

Length of hospital stay. Table VII summarizes maternal and neonatal length of hospital stay, excluding stillbirths and neonatal deaths. In 38 diabetic pregnancies, Classes B through R, a total of 203 additional antepartum hospital days were required for diabetic control or complications of pregnancy. Six infants transferred to the University of Oregon Health Sciences Center Neonatal Intensive Care Unit required a total of 82 additional hospital days.

Table VIII compares fetal outcome and protocol for Class B through R pregnancies at Good Samaritan Hospital and Medical Center for the 10 year study period and for the last 3 years with other similar studies.

Comment

The management philosophy of the private practitioners in this study contrasts sharply with the recommended protocols of other studies.[2–7] A definite interval between procedure availability and procedure utilization reflects the obstetricians "wait and see" attitude. Clinical experience, judgment, and concern for patient cost result in limited use of ancillary procedures after their acceptance.

Antepartum hospitalization was held to a minimum, averaging 7.2 days in this study compared to several weeks in others. Goldstein and associates[5] contend that costs of increased maternal hospitalization (average 28 days) are offset by decreased neonatal hospitalization (average 4 days in intensive care and 8 days in nursery). That contention is not supported by the average hospital stay of 7.3 days for infants in this study. Experienced clinical judgment and expertise can minimize ancillary procedures and hospitalization without compromising patient care or fetal well-being.

Many studies since 1949[8] have demonstrated the higher prenatal mortality rate of the male sex. The sex ratios (male:female) of 3:1 among the stillbirths and 3:2 for infants affected by RDS were not statistically significant; however, they should be noted for further study in larger numbers. Sex determination may be warranted for consideration in the future.

One of the stillborn infants, delivered of a mother with Class A diabetes, exemplifies the problem of physician awareness and antenatal diagnosis in this class. Though four of this patient's close relatives, including her mother, were diabetic, the diagnosis of diabetes was not made until the first postpartum day. Lack of definite diagnosis of Class A diabetes is evident in the incidence of 26.5% (53 cases) in this study as compared to an expected incidence of 80% (588 cases).[9]

The lack of decrease in stillbirth rates is disappointing. The average gestational age of 34.7 weeks at this

Table VIII. Comparison of Class B through R pregnancies with other similar studies

	This study (1968-1977)	*This study (1975-1977)*	*Whitely et al.*[2] *(1941-1952)*	*Drury et al.*[3] *(1951-1976)*	*Gyves et al.*[4] *(1973-1975)*	*Goldstein et al.*[5] *(1976-1977)*	*Gugliucci et al.*[6] *(1973-1974)*	*Gabbe et al.*[7] *(1971-1975)*
No. of cases	148	46	72	482	37	28	92	260
Incidence of cases	0.75%	0.75%	0.30%		0.60%		3.0%	
Stillbirths	8.8%	8.7%	9.7%	3.9%*	8.1%	0.0%	4.3%	1.1%
Neonatal deaths	6.1%	0.0%	9.7%	5.6%*	2.7%	3.6%	1.1%	3.5%
Perinatal deaths	14.8%	8.7%	19.4%	10.5%	10.8%	3.6%	5.4%	4.6%
Routine hospitalization:								
In early pregnancy	No	No	No	No	No	Yes	Yes	Yes
Predelivery	No	No	No	No	34 wk.	34 wk.	28-35 wk.	34 wk.
Average hospitalization:								
Maternal (days)	8.3	8.7				28		26
Neonatal (days)	8.3	8.8				12		

*Includes Class A diabetic patients.

occurrence may indicate the need to begin routine evaluations of fetal well-being earlier in gestation.

A minimum protocol is proposed for Class B through R diabetic pregnancies in private practice to minimize ancillary testing without compromise to patient care. At 18 weeks, prior to development of macrosomia, ultrasonography will confirm gestational age. At 28 weeks, ultrasonography evaluates fetal macrosomia, placental edema, and placental localization for future amniocentesis. Weekly contraction stress tests or nonstress tests should begin at 32 weeks. After 34 weeks, serum estriol determinations are performed two times weekly. At 37 weeks amniocentesis is performed, utilizing ultrasonography if necessary. Fetal pulmonary maturation should be determined by more than one parameter, such as lecithin-sphingomyelin ratio and palmitic acid. Delivery should be effected without delay when evidence of fetal pulmonary maturity is present. Clinical judgment should dictate deviation from protocol with complications of pregnancy or diabetes. Without evidence of progression of disease or complications, Class A diabetic pregnancies should be managed expectantly and conservatively and delivered at term.

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Discussion

Dr. Leon P. Fox, San Jose, California. Dr. Corwin has ably presented in retrospect a significant experience in the management of pregnancy complicated by diabetes mellitus in a private-practice setting. In my opinion this depicts fairly accurately the current situation in most such environments. It certainly is similar to my community's efforts. His data indicate that stillbirths continue at the same rate though neonatal deaths recently have been eliminated. Comparative statistics gathered at high-risk obstetric centers indicate much better results. The bottom line in diabetic pregnancies is ideally to erase all perinatal deaths and this currently appears to depend upon superior expensive antenatal care of these patients. Dr. Corwin in an effort to improve results has now proposed a standard protocol to his associates which no doubt will be effective.

The name of the game is early diagnosis; accurate determinations of fetal age in the second trimester; continuous monitoring of blood sugar levels on a

Table I. Pertinent comparable costs—1940 and 1978

	1940	*1978*	*Change*
Obstetrician (cost in dollars)	75	650	(+) 8.5X
Hospital (cost in dollars)	50	1,500	(+)30.0X
Home (cost in dollars)	13,000	65,000	(+) 5.0X
Automobile (cost in dollars)	1,200	13,000	(+)10.8X
Salaries (nurses, etc.) (cost in dollars)	65	1,100	(+)18.0X
Diabetic perinatal mortality rate (%)	31	4.2	(−) 7.0X

monthly basis; team approach to meticulous therapy, utilizing obstetrically oriented diabetologists, currently knowledgeable obstetricians, and consulting perinatologists-neonatologists in a facility with immediately available laboratory technology and appropriate monitoring equipment in all parameters; and, last but not least, a developed protocol for complete education and counseling of the patient throughout her pregnancy.

Although all of us are continually interested in cost control in the care of these and other patients, cost must not be the reason for withholding these absolutely necessary services from the pregnant diabetic patient. Diabetes has long been recognized as a "rich man's disease" and will continue to be so. Recent estimates of the increased expense of ideal high-risk care of these diabetic patients is approximately $6,500 or more. The challenge, therefore, is to seek ways of providing this same care at a lower cost. Schneider in Memphis has done something about this, and in as yet unpublished material has described a group of patients managed in a high-risk public hospital setting on a carefully controlled out patient basis. Utilizing the protocol mentioned with some changes, all patients are screened for diabetes clinically as usual early in the second trimester, depending upon the blood sugar level 2 hours after a meal. The diabetic patients are classified and placed on a continuing, comprehensive educational and counseling program. This includes instruction in self-testing of postprandial blood sugar level each month in Class A patients and three times daily or more in insulin-dependent patients by use of the reflectometer.

Early in the second trimester clinical and sonographic efforts are made to determine fetal age. This is confirmed after the twenty-eighth week. From the thirty-second week patients are seen on a weekly basis with close attention to fetal well-being and, of course, diabetic control. Nonstress testing at home and in the outpatient department is charted and depended upon. If the fetal age has become apparently confirmed, at 38 weeks a lecithin/sphingomyelin (L/S) ratio is obtained and a phosphatidylglycerol test is done. If the L/S ratio is above 2 and phosphatidylglycerol is present there will be no RDS problem and delivery is carried out in the indicated manner. All newborn infants must have intensive care for 2 or 3 days or more.

Only sick patients are hospitalized and of course estriol determinations, oxytocin challenge tests, and other appropriate tests are done. Dr. Corwin's perinatal loss in some 108 patients averaging 7.1 days of hospitalization was 37/1,000, there being one stillbirth and three neonatal deaths.

The hospitalization costs compare with Dr. Corwin's data and the perinatal results are similar to the long-term hospital stay data presented. Dr. Schneider has stated that "A difference to be a difference must make a difference," and certainly this program does so.

I believe all insulin-dependent mothers should be delivered in a high-risk maternity center by their own obstetricians who can make use of all the facilities necessary to provide the intensive care that is imperative to the mother and newborn infant.

I would like to say just a word about health care costs. Our politicians and other propagandists get carried away in their selective separation of health care costs from the general economy trends and, with you, I become very irritated by these tactics to force us into government control when everyone knows that everything done by government is always the most expensive. In 1940, when my first child was born, obstetricians were charging $75 to $100 for total usual care and $150 if a cesarean section was done. The hospital bill was $50 for 10 days. My automobile cost $1,200 and my home $13,000. Today, in the same area, the obstetrician averages $650 for usual care and $900 for total care plus cesarean section. A comparable automobile now costs $13,000. The usual 2 to 3 day hospital stay is about $1,500, including anesthesia, mostly due to salaries and equipment. If the stay should reach 10 days the total would be $3,500 and the same home now costs $65,000. Inflation has made our numbers meaningless and our currency valueless. Table I indicates the cost changes during the past 38 years.

During this time period the percentage of perinatal deaths in diabetic patients has decreased sevenfold and the average income has increased thirteenfold. When I hear a patient complain about the $6,500 extra costs for the care in her diabetic pregnancy I ask her what she paid for her automobile and she is reminded promptly of her priorities. We still continue to save babies in better conditions and we will continue to devise methods of cost control if we are permitted to do so.

Dr. Robert H. Gregg, Covina, California. In reviewing the literature and Dr. Corwin's article, I would like to add one other aspect to the equation of diabetes complicated by pregnancy leading to the bottom line. Several of us have had brief conversations, here at Salishan, on the future social, cultural, and medical ramifications of scientific progress. As far as we know, exclusive of Divine Providence, man is the only living thing who can, and has been able to, *by choice* seek the cause and effect of things and, again through choice, to change his environment, both internal and external, and particularly in this century to begin to effect con-

trol over his internal milieu. On the surface, this may seem like a very basic human need and the thing to do. Of course this is what science and the practice of medicine are all about, that is, to treat the infirmed, prevent disability and disease, and promote health and well-being, and indeed, in the long run, maybe to engineer a so-called "super human being" and even a "super race," which was attempted about 40 years ago. But in our mad dash to overcome and alleviate the obvious need, are we taking into consideration the natural and biological balances that are necessary to sustain, maintain, and perpetuate the species on this earth? Are we asking ourselves the very serious, more significant and poignant questions, to what extent should the diabetic patient in this instance have the same benefits of normal life expectancy, health and happiness, children, and so forth? Should they not be part of the human race also? But in the final analysis where do our efforts stop? How far should they go? Should they stop at all?

DR. CORWIN (Closing). I heartily agree with everything Dr. Fox said.

I am not quite sure how to answer Dr. Gregg. This has been an age-old argument, philosophical mostly, regarding the eugenic considerations of diabetes. I think it probably is the same with any other disease state having genetic implications. As of this juncture, in any case, I believe we are charged with the responsibility to do the best we can with any pregnancy, regardless of the nature of the pathologic or unusual state the patient may have, assuming the patient understands the inherent risks, hazards, and future consequences. I would like to emphasize one thing that Dr. Fox brought out—and that I did not emphasize in my paper—I am still, and I believe all of us are, a firm believer in the team approach to the diabetic pregnancy. I feel it is extremely important to have the cooperation of three groups—pediatricians, obstetricians, and internists (ideally diabetologists). Apparent suboptimal utilization of ancillary testing in our institution may be the result of suboptimal medical records. All of you, having done research involving only the medical records, appreciate the fact that medical records are often incomplete—excepting your own.

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Urinary tract endometriosis: Enigmas in diagnosis and management

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The diagnosis and management of endometriosis presents several enigmas. This review, of eight patients with endometriosis involving the urinary tract, from three large clinical services in the City of Los Angeles, highlights some very difficult problems. Not only diagnostic errors but also inappropriate conservatism and inadequate surveillance have led to compromised function, resection, and/or destruction of the kidneys, ureters, or bladder. The series indicates those findings which are likely to result in urinary tract destruction and points out those clinical situations in which delays or conservative management must be undertaken only with pressing indications and then only with continued and careful surveillance.

ENDOMETRIOSIS with significant involvement of the urinary tract is not particularly uncommon. Involvement of the urinary bladder is more common, but associated ureteral obstruction presents a more serious threat to renal function. The magnitude of this threat has become apparent only in recent years. In 1960, a review of the world literature uncovered only 15 reported cases of endometriotic obstruction of the ureter. By 1965, Kerr's[2] review brought the total up to 47 and, in 1974, Durfee, in discussing Langmade's[3] report of five cases before this Society, reported 85 such cases in the literature. Reports since then[4–9] and the present series bring the total to over 100 patients with ureteral obstruction caused by endometriosis. It is quite probable that there is a far larger number unreported and even unrecognized.

In the largest series of endometriosis with ureteral obstruction (11 cases collected over a 40 year period), Stanley and associates[10] emphasized that the relative paucity of specific diagnostic symptoms or physical signs augured against an early appreciation of a threat to the urinary tract. Catamenia-associated symptoms and even microscopic hematuria represent diagnostic exceptions. Generally excretory urograms taken in the investigation of backache, headache, hypertension, or a pelvic mass bring a suspicion of endometriosis into focus. Occasionally cystoscopy, retrograde ureteropyelograms, and even laparoscopy fail to indicate endometriosis. The present report demonstrates the importance of paying careful attention to the uterosacral ligaments in evaluating ureteral obstruction in women of menstrual age. It is apparent that when the cardinal and the uterosacral ligaments are involved with endometriosis, the ureters and kidneys are at risk and careful surveillance is in order. As indicated by Kerr,[2] Meigs emphasized this point four decades ago.

Most authors[2, 3] indicate that prudent management of ureteral obstruction from endometriosis includes relief of obstruction (ureteral lysis, implantation, or diversion), resection of endometriosis, and surgical castration (bilateral oophorectomy and hysterectomy). They emphasize that inordinate delays and what Green[11] terms "conservationistic" surgery generally lead to further problems. Such optimal management presents no great conflict if the patient is multiparous and over 40 years of age. The conflicts arise when the

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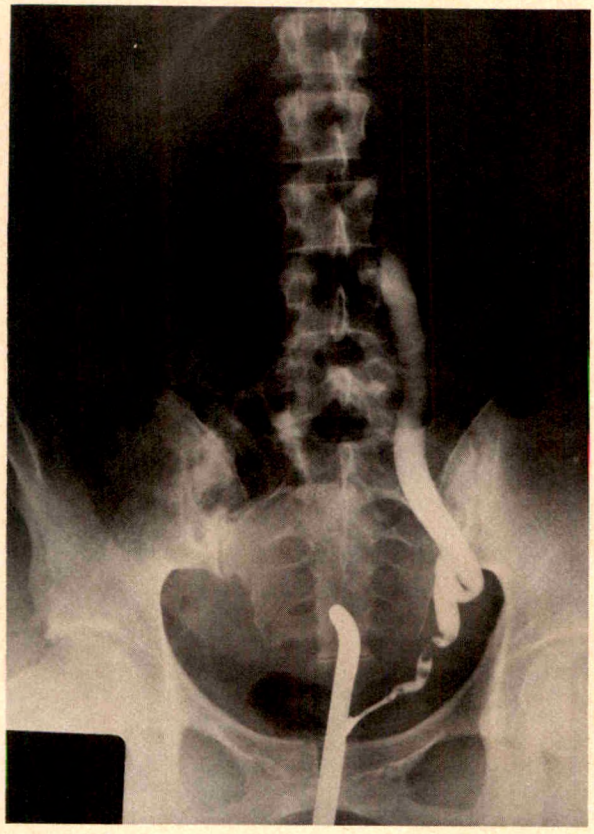


Fig. 1. Retrograde ureteropyelography demonstrating stenotic but barely patent distal left ureter in Case No. 1.

patient is in her twenties and strongly desires more children. In the present series an unusually young group of women, highly desirous of maintaining fertility, posed some difficult problems.

Clinical material

Patient records of the Cedars-Sinai, Los Angeles County–University of Southern California, and the University of California, Los Angeles, Medical Centers were searched for patients operated upon for endometriosis with ureteral obstruction. Eight such patients, operated upon in the past 8 years, are listed in Table I. Seven were operated upon at the University of California, Los Angeles, Hospital. The record search extending back to 1965 revealed no patients operated upon for this condition at Cedars-Sinai and only one (Case No. 4) at the Los Angeles County–University of Southern California Hospital. One of the patients operated upon at the University of California, Los Angeles, Hospital (Case No. 5) had previously had a laparoscopic exploration at Cedars-Sinai.

Of the eight patients, two (Cases 1 and 7) were over 40 years of age when operated upon and were the only

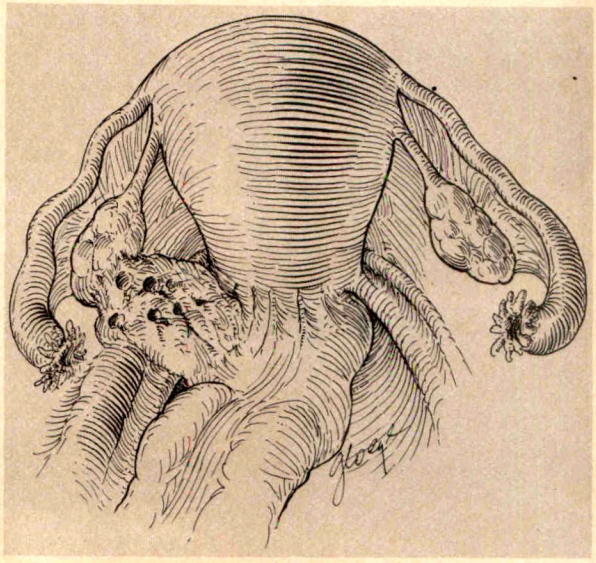


Fig. 2. Operative findings in Case No. 1, showing relatively restricted extent of endometriosis involving the left ovary and uterosacral ligament. The proximal ureter, as opposed to that in Case No. 5, is widely dilated.

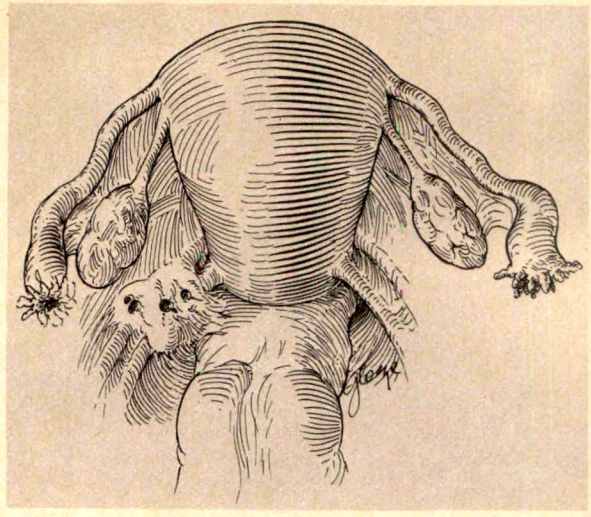


Fig. 3. Operative findings in Case No. 5. Note that both ovaries and tubes are not involved. The endometrioma, not impressive on the surface, extended deeply retroperitoneal and was confined to the left uterosacral ligament, the cardinal ligament fully occupying the "web" and the lateral wall of the rectosigmoid colon, and completely obstructing the distal left ureter. Since the kidney was no longer functional the ureter was not distended.

multiparous patients in the group. The next oldest patient (Case No. 5) was 33, had one child, was divorced, and hoped for remarriage and more children. The others (Cases 2, 3, 4, 6, and 8) were nulliparous and their ages ranged from 32 down to 21 years.

Case No. 1 illustrates very well the diagnostic prob-

Table I. Clinical data in eight cases of endometriosis

Case No.	*Year*	*History and diagnostic appraisal*
1 (age 43, gravida 2, para 2)	1969	Backache, negative myelogram
	1970	Dysmenorrhea and postcoital back pain. Endometriosis suspected. Progestational suppression
	1971 (UCLA)	3-4 cm mass at base of left broad ligament. Intravenous pyelograms showed left hydronephrosis
2 (age 30, gravida 0)	1969	Dysmenorrhea and infertility, 3 yr. Resection of rt. ovarian endometrioma
	1970	Progressive dysmenorrhea and dyschezia
	1971 (UCLA)	8 cm left adnexal mass. Intravenous pyelograms showed obstruction distal to left ureter
3 (age 32, gravida 0)	1967-73	Oral contraception. Blood pressure 120/70
	1974	Dysmenorrhea and premenstrual dysuria
	1975 (Indiana U.)	Intravenous pyelograms showed medial displacement of both ureters. Laparoscopy showed extensive pelvic endometriosis. Renal scans showed hydronephrosis, hydroureter, and delayed excretion. Progestational suppression, followed by resolution of hydronephrosis
	1976 (UCLA)	Dysmenorrhea and recurrence of lower abd. pain on cessation of menstrual suppression. Blood pressure 130/90
4 (age 25, gravida 0)	1977 (USC)	2 yr. history of flank pain, hematuria, and dysmenorrhea, 2 mo. history of dizzy spells and hypertension. Pelvic examination showed bluish cyst in right fornix, fixed retroversion of uterus, uterosacral nodularity. Blood pressure 170/120, 4+ albuminuria, microscopic hematuria, creatinine 1.3 mg/100 ml, aldosterone 24 mcg/24 hr. Aortograms showed 1.5 mm of right renal cortex with marked hydronephrosis
5 (age 33, divorced, gravida 4, para 1, 3 therapeutic abortions)	1977 (Cedars-Sinai)	5 mo. history of headache and hypertension. Intravenous pyelogram showed delayed left renal function and hydronephrosis. Blood pressure 180/110. Minimal uptake of left kidney on renal scan. Laparoscopy showed no endometriosis. Arteriogram showed minimal left renal cortex visualized.
	1977 (UCLA)	Blood pressure 110/65 (asymptomatic except for dyschezia and dyspareunia). Pelvic examination showed 4-5 cm tender, fixed, firm mass to left of and posterior to the uterus and cervix
6 (age 26, gravida 0)	1978 (UCLA)	1 yr. history of progressive dysmenorrhea with LLQ abdominal pain despite oral contraceptives. 3-4 mo. of dysuria with menses. Pelvic examination showed tender, nodular uterosacral ligaments with 2 by 6 cm nodule anterior to rectum, 3 by 5 cm irregular, firm mass anterior to uterus. Pelvic ultrasound showed mass impinging on bladder. Intravenous pyelograms showed filling defect in bladder and right hydronephrosis
7 (age 44, gravida 3, para 2)	1962 (Philippines)	RLQ pain. RSO for endometrioma. Progestational suppression of menses
	1965	Resection of left ovarian endometrioma
	1967-1974	Two term births
	1977	RLQ pain and intestinal obstruction. Resection of endometriosis, segmental small bowel resection, appendectomy
	(Feb.) 1978 (Philippines)	TAH and LSO (no menopausal symptoms)
	(Aug.) 1978 (UCLA)	RLQ and RUQ abdominal pain. FSH not elevated. Sonogram showed 9 by 9 cm right pelvic cyst. Intravenous pyelogram showed right hydronephrosis
8 (age 21, gravida 0)	1975 (UCLA)	Dysmenorrhea despite oral contraceptives. Pelvic examination showed tender, nodular right uterosacral ligament. Laparoscopic biopsy showed endometriosis
	1976 and 1977	3-4 cm tender mass in area of right uterosacral ligament
	1978	Angulation, medial displacement, and impaired drainage of right ureter

TAH = Total abdominal hysterectomy; BSO = bilateral salpingo-oophorectomy; LSO = left salpingo-oophorectomy; LLQ = left lower quadrant; RLQ = right lower quadrant; RSO = right salpingo-oophorectomy; RUQ = right upper quadrant; FSH = follicle-stimulating hormone.

lems. The patient suffered for 2 years with severe back pain and was investigated thoroughly for discogenic disease, including myelograms before the onset of dysmenorrhea, and a mass in the region of the left uterosacral ligament finally led to the presumptive diagnosis of endometriosis. Intravenous urography revealed massive left hydronephrosis and retrograde pyeloureterography confirmed the marked stenosis of the ureter 2 to 4 cm from the vesical orifice with marked ureteral dilatation above the stenosis (Fig. 1). At operation a single, solid 4 cm endometrioma involving the left ovary and uterosacral ligament engulfed the left ureter with a tensely dilated ureter superior to the mass (Fig. 2). At her age and parity management presented no problem. The endometrioma was resected and total hysterectomy, bilateral salpingo-oopho-

Operative findings	*Operative procedure*	*Postoperative course*
Endometriosis restricted to left ovary and uterosacral ligament, with massively dilated ureter. Stenosis 2-3 cm above ureterovesical junction	TAH and BSO. Resection of distal third of left ureter. Left ureteroneocystotomy	Normal renal function. Slight urinary reflux. No problems up to 1978
Endometriosis of left ovary and uterosacral ligament	TAH and LSO. Left ureteral lysis	Normal intravenous pyelogram. Asymptomatic with estrogens up to 1978
Retrograde pyelograms showed medial deviation of right ureter with scarred encasement from 4 to 8 cm from ureterovesical junction. Extensive endometriosis involving both ovaries, uterosacral ligaments, rectosigmoid colon, bilateral periureteral involvement, appendiceal involvement	Bilateral ureteral lysis. TAH and BSO	Uneventful postoperative course. Blood pressure 120/70. Norlutate suppression. Death 4 mo. postoperatively in auto/train accident
Endometriosis of ovaries and uterosacral ligaments. Obstructed right ureter 2 cm from ureterovesical junction	TAH and BSO. Right ureteroneocystotomy	Uneventful postoperative course. Intravenous pyelogram showed atrophy of right kidney. Blood pressure 120/80
Isolated focus of endometriosis involving base of left broad ligament, left uterosacral ligament, and left lateral portion of rectosigmoid colon—largely extraperitoneal with puckering of overlying peritoneum. Frozen section revealed endometriosis obstructing left ureter. Uterus, tubes, and ovaries not involved	Resection of left kidney and ureter. Resection of left parametrium ("the web") with left uterosacral ligament and wedge resection of left lateral wall of rectosigmoid colon. Left uterine vessels removed but not left ovarian ligament. Left round ligament suspension of uterus. Appendectomy and curettage	Uneventful postoperative course. Asymptomatic. Uses diaphragm
Cystoscopy showed 2-3 cm mass in right superolateral aspect of bladder wall. Urothelium intact. Large focus of endometriosis involving omentum, wall of transverse colon, wall of bladder, and anterior uterine peritoneal surface	Open resection of bladder wall, omental resection, segmental resection of transverse colon. Right ureteral lysis. Presacral neurectomy	Uneventful postoperative course
Extensive endometriosis with endometrioma in right pelvis involving the right ureter, right base of urinary bladder and wall of rectosigmoid colon	Resection of right ovarian endometrioma, proximal right ureterostomy with placement of ureteral catheter, ureteral lysis, resection of endometriosis of bladder wall and rectosigmoid colon	Uneventful, with removal of ureteral stint on second postoperative day and suprapubic catheter on sixth postoperative day. Discharged with progestational menstrual suppression
3-4 cm endometrioma of right uterosacral ligament	Right ureterolysis, resection of endometrioma of uterosacral ligaments	Uneventful postoperative course

rectomy, appendectomy, and left uteroneocystotomy were performed. In the 8 years of follow-up she has had no problems, intravenous urography is normal and there is very slight left ureteral reflux.

In Case 2, after several years of severe dysmenorrhea and infertility, the patient, at the age of 28, underwent right salpingo-oophorectomy for an endometrioma of the right ovary. After two additional years of progressive dysmenorrhea and dyschezia, she developed a cystic left adnexal mass. Intravenous urography showed partial obstruction of the distal left ureter. At surgery she was noted to have extensive endometriosis of the left ovary, left uterosacral ligament, and the posterior aspect of the bladder. Because of the disabling symptoms and the extensive distribution of the endometriosis, a right salpingo-oophorectomy, total hysterectomy, and ureteral lysis were performed along with resection of all grossly apparent endometriosis.

Case No. 3 had previously been reported[5] as demonstrating the regression of ureteral obstruction with

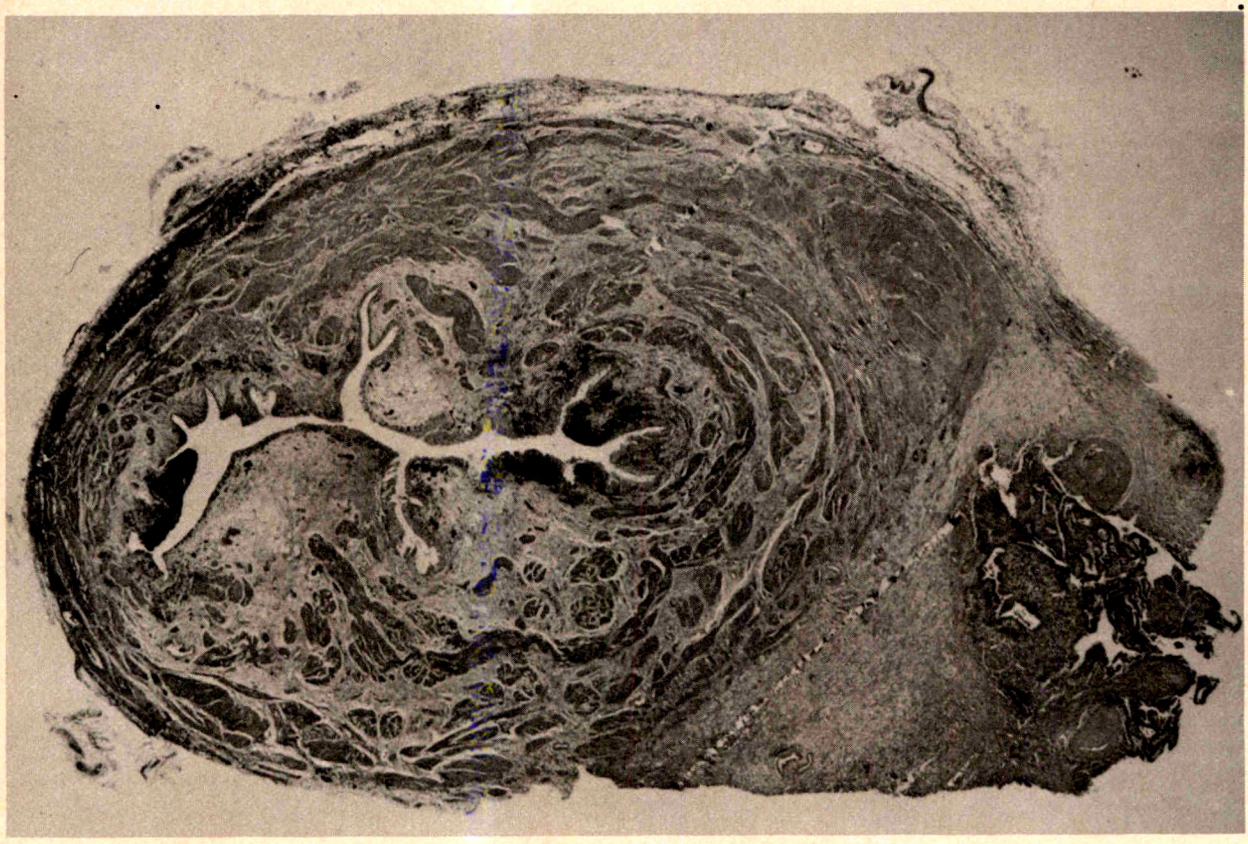


Fig. 4. Area of endometriosis beside collapsed ureter (obstructed distally) in Case No. 5. Kidney was nonfunctional.

progestational suppression of menses. The following year, with return of symptoms and the development of hydronephrosis on the opposite side, and despite her nulliparity, she underwent bilateral salpingo-oophorectomy, total hysterectomy, appendectomy, resection of endometriomas, and bilateral ureteral lysis. Postoperatively she had normal ureters by intravenous pyelograms with uneventful follow-up to 4 months, when she was killed in an accident.

In Case No. 4, the patient was 25 years old and nulliparous, with symptoms and findings suggestive of extensive endometriosis and right renal cortical destruction. A thorough study of renal function indicated minimal function of the right kidney. Because of extensive endometriosis bilateral salpingo-oophorectomy, total abdominal hysterectomy, resection of endometriomas, and a right ureteroneocystotomy were done. Six weeks postoperatively the blood pressure returned to normal and the renal study showed atrophy of the right kidney with a patent right ureter.

In Case No. 5 the patient presented with a 1 year history of left pelvic pain, dyspareunia, and dyschezia and 5 months of headache and hypertension. Symptoms and findings were those of left renal cortical destruction and the diagnosis of endometriosis could not be made even on laparoscopy. During a period of observation the headache and hypertension disappeared but dyschezia and dyspareuia persisted. A firm mass was noted at the base of the left broad ligament and left uterosacral ligament. At operation a single 4 cm solid retroperitoneal mass engulfed and completely obstructed the left ureter (Fig. 3). With complete destruction of the left renal cortex the ureter was no longer dilated proximal to the obstruction. She was subjected to a left ureteronephrectomy including resection of the endometrioma (Fig. 4), a segment of the rectocolonic wall, the left uterosacral ligament, the left cardinal ligament, and the left uterine blood vessels. Because of the restricted extent of the endometriosis and her strong desire for maintaining fertility, the ovaries, tubes, and uterus were left intact. Obviously, she is scheduled for careful periodic surveillance.

In Case No. 6, the patient was a 26-year-old nulligravid woman with a 6 year history of dysmenorrhea

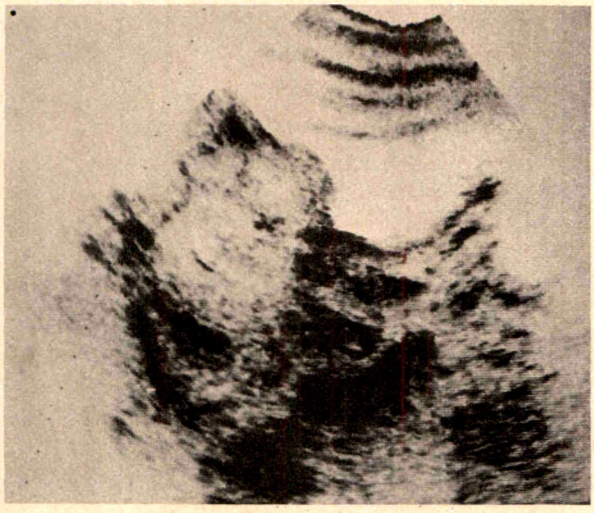


Fig. 5. Midline sagittal sonogram in Case No. 6 showing mass anterior to uterus involving wall of bladder.

and 3 to 4 months of catemenial dysuria. On examination she was found to have a mass in the region of the right uterosacral ligament and another mass anterior to the uterus. Sonography (Fig. 5), intravenous urography (Fig. 6), and cystoscopy were helpful in delineating the problem. Operative exploration revealed that the tubes and ovaries were not involved (Figs. 7A and 7B) and, in view of her strong desire for children, the endometriosis, though moderately extensive and involving the transverse colon, the bladder, and the uterine wall, was resected with repair of the involved structures and ureteral lysis. This does not represent the safest management of endometriosis of this extent and careful surveillance is mandatory.

Case No. 7 represents a serious urologic problem resulting from inadequate resection of endometriomas in a multiparous woman in her 40's. Fig. 8, *A* and *B*, illustrates the marked ureteral obstruction. Quite obviously residual ovarian tissue was left since a corpus luteum was found in the tissue containing residual endometriosis. On this occasion it was necessary to perform a right ureterostomy in order to ensure an adequate ureteral lumen during the ureteral lysis. Although the initial postoperative studies show a normal urinary tract, sufficient time has not elapsed to ensure integrity of the right ureter.

Case No. 8 indicates the need for careful continued surveillance of patients with endometriosis of the uterosacral ligament. Two years prior to exploratory surgery, this 21-year-old nulligravid woman had endometriosis confirmed at laparoscopic biopsy of the right uterosacral ligament. The ovaries were not involved and no peritoneal endometriosis could be seen

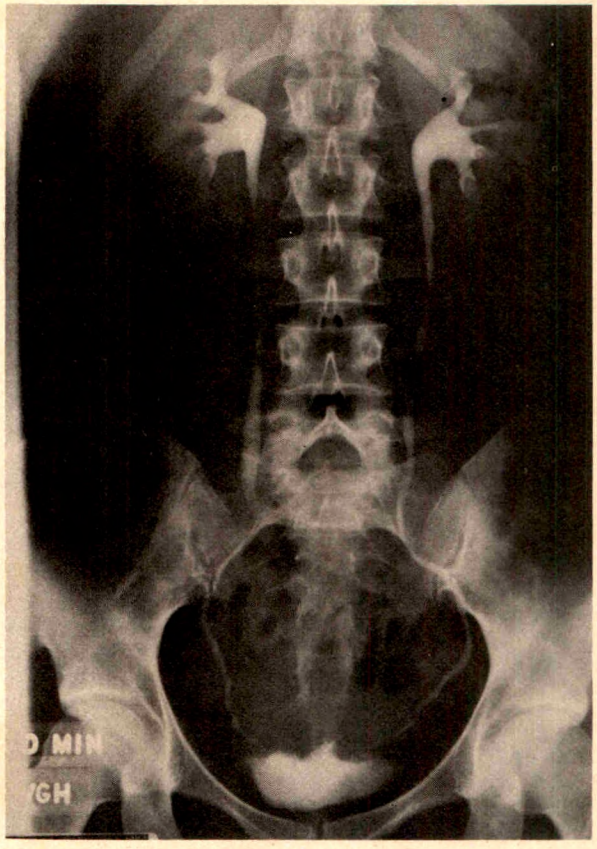


Fig. 6. Intravenous urography at 10 minutes in Case No. 6, showing involvement of the bladder wall with ureteral dilatation above pelvic brim.

outside the cul-de-sac (Fig. 9). Continued observation disclosed a gradually enlarging 4 cm mass in the right uterosacral ligament, which was confirmed by sonography, and intravenous urography showed medial displacement and angulation of the distal ureter with partially obstructed drainage (Fig. 10, *A*). At exploration a 3 by 4 cm endometrioma was found in the right uterosacral ligament and, because of the fairly restricted extent of the disease and a strong desire for children, the procedure was restricted to resection of endometriosis, ureteral lysis, and appendectomy. In such cases careful surveillance is mandatory to ensure continued renal integrity.

In all, three (or possibly four since in Case No. 6 there was a single but extensive endometrioma) of these eight patients had restricted foci of endometriosis primarily involving the uterosacral ligament and/or cardinal ligaments. In three of these instances, despite the threat of future renal problems, the patient was not castrated and the possibility of childbearing was maintained.

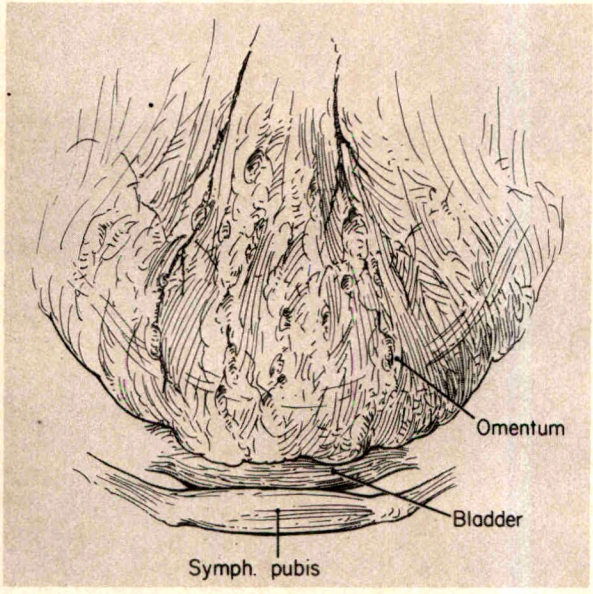


Fig. 7A. Endometrioma in Case No. 6, showing massively adherent omentum.

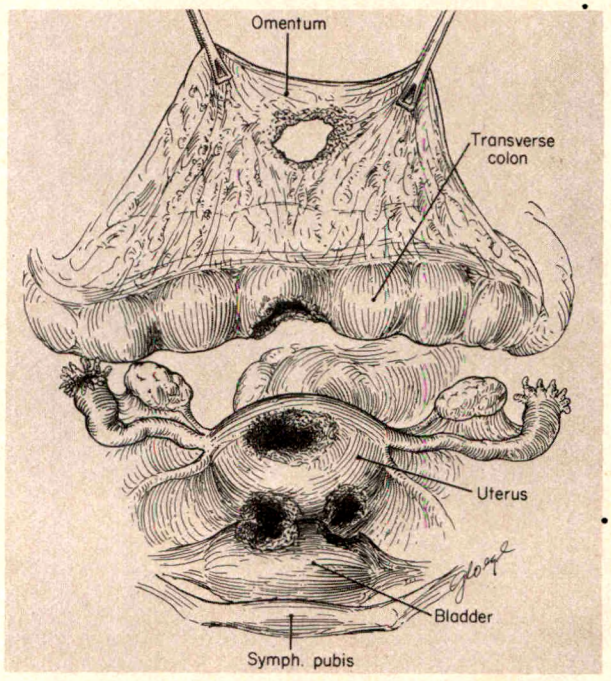


Fig. 7B. Case No. 6 after full operative dissection.

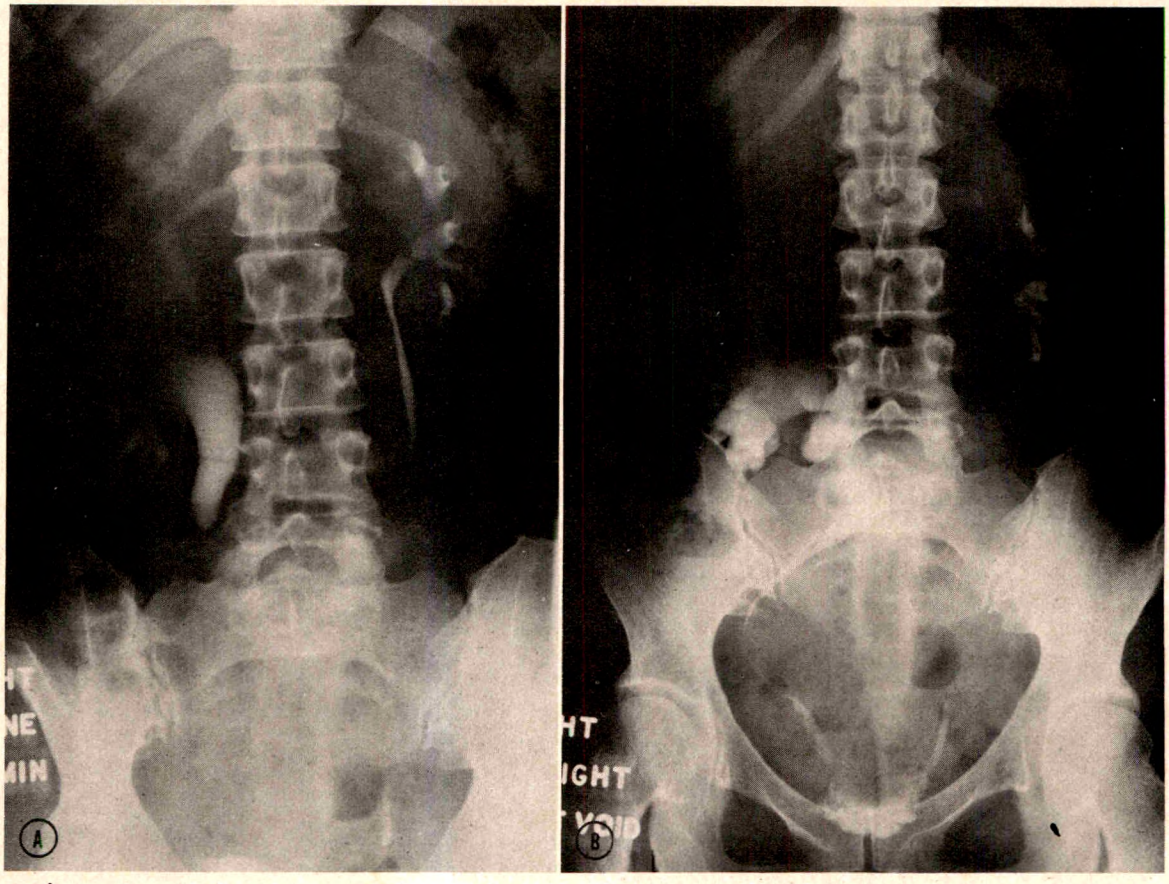


Fig. 8. Intravenous urography at 10 minutes *(A)* in Case No. 7, showing marked right hydronephrosis and high obstruction of the pelvic ureter and upright film after voiding *(B)*, showing ureter displaced and compressed by endometrioma.

Comment

Endometriosis involving the urinary tract is not a completely benign condition. This series and others[2, 10] indicate that 25% of kidneys are lost when endometriosis obstructs the ureter. Ureteral obstruction may occur with extensive pelvic endometriosis but is most likely to occur with minimal extent of the disease when the uterosacral ligaments are involved. The experience reported here shows three cases of ureteral obstruction, including the loss of a kidney, with endometriosis which was virtually restricted to the uterosacral ligaments. Careful appraisal of the uterosacral ligaments and urologic evaluation at least by intravenous urography should be carried out if endometriosis is to be managed expectantly.

Most instances of ureteral obstruction occur insidiously with less than half of the patients showing symptoms of upper urinary tract dysfunction. Headache, backache, and hypertension point to the likelihood of upper urinary tract obstruction. Pyelonephritis is seldom associated with endometriotic obstruction and renal death may be relatively silent. Too often, as in

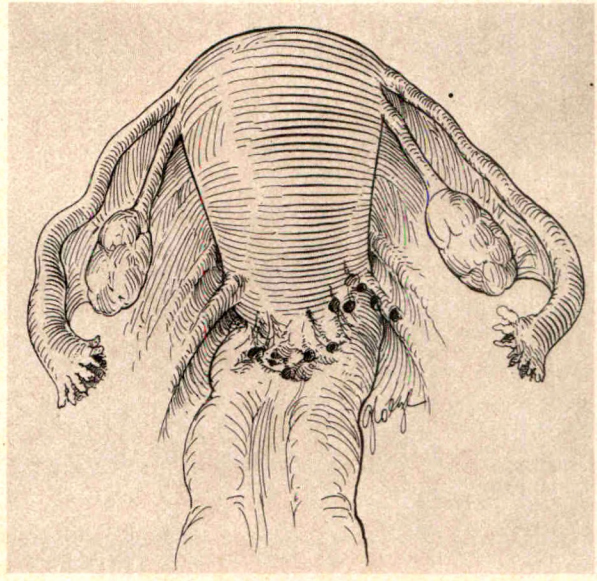


Fig. 9. Minimal endometriosis involving the cul-de-sac and right uterosacral ligament proved by translaparoscopic biopsy 3 years prior to ureteral lysis for angulation, fixation, and deviation of right ureter by endometrioma.

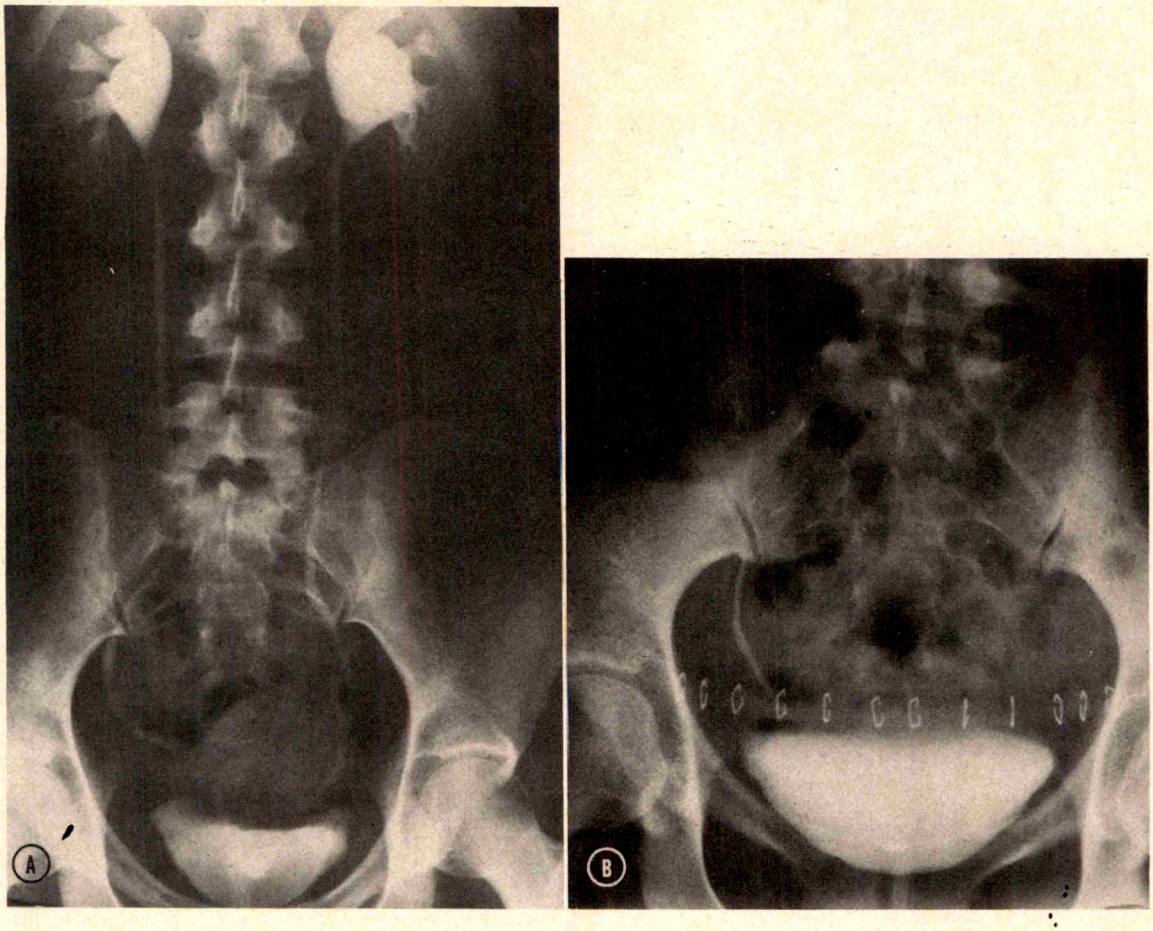


Fig. 10. Intravenous urography at 12 minutes *(A)* in Case No. 8, showing deviation and obstructed drainage of the right ureter and normal course of right ureter following operation *(B)*.

Cases 4 and 5, renal cortical destruction is suggested by hypertension and headaches and confirmed by greatly delayed or absent kidney function on intravenous urography with renal arteriography demonstrating a minimal renal cortex. Subsidence of hypertension and reduction of proximal ureteral distention is not necessarily a sign of improvement and may, as in Case No. 5, indicate fairly complete renal cortical destruction. Ureteral implantation in such instances has a poor chance of success.

Following a reasonable parity and especially if the patient is over 35 years of age, endometriosis should be treated aggressively. This tenet is especially true if there is urinary tract involvement. Under these circumstances, as others have wisely proclaimed,[2, 3] there is no place for conservationistic management, as was well illustrated in Case No. 7. Less than resection of the endometriomas, relief of urinary tract obstruction, and ovarian ablation does not represent conservative or prudent management. It represents an invitation to further difficulties and imposes a 25% chance for the loss of a kidney. If, in the interests of continued reproductive capability, the endometriosis is resected and the ureteral obstruction is relieved but ovarian function is maintained, then periodic surveillance of urinary integrity is well advised.

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Discussion

DR. CHARLES F. LANGMADE, Pasadena, California. Nothing is absolute, nothing is 100%, and Dr. Moore has pointed out to us that total removal of all ovarian tissue, hysterectomy, and lysis of ureteral obstruction is not always the best form of management as we suggested in 1974. When child-bearing must be preserved, the ideal method of management must be compromised and this part of the paper is a real contribution.

Surely in the young 21-year-old nulliparous patient, Case No. 8 in the series, attention must be given to her desires and her wishes for having a family. On the other hand, the 44-year-old woman, para 2, gravida 3, with a long history of endometriosis and sterility should be treated quite differently. Surgical exploration in Case 7 revealed extensive disease requiring resection of the bladder, rectosigmoid bowel, and an endometrioma of the ovary. I would like to ask Dr. Moore how it was decided to resect the endometrioma rather than remove all the ovarian tissue. The patient had already undergone hysterectomy. She may have been adamant in regard to definitive complete surgery; however, ideally she should have had all ovarian tissue removed and retroperitoneal exploration to be sure that this was accomplished.

In Cases 1, 2, 3, and 4, all the ovaries were removed and to this we agree. In Case No. 5, a 33-year-old woman gravida 4, para 1, therapeutic abortions 3, with hypertension had symptoms of endometriosis for 4 years. At operation, she required resection of the left kidney, ureter, and rectosigmoid bowel and, in general, had extensive disease. We must ask ourselves again what the chances are for this patient to conceive. At operation, the patient of Case No. 6 required resection of the bladder, omentum, and transverse colon and ureteral lysis and her possible child-bearing function was preserved.

We agree with Dr. Moore's management of Cases 1, 2, 3, 4, and 8. Cases 5, 6, and 7, in our opinion, should have had complete removal of all ovarian tissue. I would like to ask Dr. Moore if these three patients were strongly advised to have complete surgery for their disease. If they were and refused then we understand the management. We now have seven cases of ureteral obstruction due to endometriosis and in no instance was definitive surgery refused.

There are only a few controversial points put forth in the paper. The term "castration" should be abandoned. Somehow this eventually gets through to the patient and then sets a very different stage than the careful explanation that removal of all ovarian tissue should be done and the endocrine secretion can safely be supplied by oral estrogens. Dr. Moore rightly uses oral estrogens following definitive surgery for endometriosis. It has been suggested that estrogens will stimulate the remaining endometrial tissue, which is not true if

both ovaries have been removed. It remains questionable if Norlutate "suppresses" endometrial tissue after ovarian removal. Laparoscopic examination in a patient with palpable disease and an obstructed ureter is probably not indicated unless for teaching purposes. In many instances and in Dr. Moore's report, the disease is almost a retroperitoneal desmoid reaction and will not be seen on laparoscopy.

Entering a partially obstructed ureter with a nonfunctioning or hydronephrotic kidney will lead to severe infection in some instances and simple lysis of the obstruction would seem preferable. Dr. Moore encountered no such problem in his cases requiring ureteral resection. Presacral neurectomy is of questionable value in extensive adnexal disease.

The diagnosis of endometriosis continues to be missed, but it would seem preferable to have the history and minimal pelvic findings lead us to ordering an intravenous pyelogram rather than the intravenous pyelogram leading us to the diagnosis. Symptoms, however, may be very sparse. In one case reported in 1974, endometriosis extended through the vagina and bladder to both side walls and destroyed one kidney, yet she had not one day of pain. We should order more intravenous pyelograms in patients with endometriosis.

The postoperative intravenous pyelogram in Case No. 8 appears little changed from the preoperative one. The dye is still retained on the involved side and the course seems about the same. I would like to ask Dr. Moore if subsequent studies showed this to be completely resolved.

It is heartening to hear such a paper coming from three large institutions; University of California, Los Angeles, Cedars of Sinai and Los Angeles County–University of Southern California. Endometriosis imposes sterility on a great number of real achievers in our country today. I am unaware of any large-scale, long-term research program to eradicate the disease. Dr. Moore and his co-authors are in positions to do this and I sincerely hope further studies will be done.

DR. EDWARD C. HILL, San Francisco, California. It has been my impression that in most instances in which the ureter is obstructed by an endometriotic process, it does so by compression, rather than by actual involvement of the ureteral wall. This was borne out in the microscopic section of the ureter that Dr. Moore presented. I would ask Dr. Moore whether in his experience, in any of these cases, particularly those in which there was a ureteroneocystostomy, there was actual involvement of the ureteral wall itself.

DR. ERNEST A. WATERMAN, Portland, Oregon. A fascinating series of patients with endometriosis was presented. None of these apparently had a history of previous use of an intrauterine contraceptive device. If it is valid that retrograde menstration is a possible etiologic factor in the development of endometriosis, and since one of the optimal times for intrauterine contraceptive device insertion is during the menses, does Dr. Moore feel that we may anticipate, in the near future, an increase in the incidence of endometriosis in our practices?

DR. CHARLES WEBER, La Jolla, California. I would like to ask Dr. Moore whether or not he actually had anticipated urinary tract involvement in any of the cases reported, and if so how many?

DR. EDWIN T. MACCAMY, Seattle, Washington. Dr. Moore, what is dyschezia? Do you always anticipate having to enter the bowel; if so, how do you prepare the bowel?

DR. GILBERT A. WEBB, San Francisco, California. During my residency, I had the pleasure of assisting Dr. Trout—late of this Society—on a case of pelvic endometriosis where the left ureter was involved. What makes this case unique was that the patient had had a left nephrectomy in the previous year because of persistent hematuria. This had been studied by the urologist and indentified as coming from the left ureteral orifice. An assumption was made of a small obscure cancer of the left kidney as the intravenous pyelogram and retrograde studies were normal. Histologic studies of the removed specimen failed to reveal any malignancy. Thus the accurate diagnosis was not established until laparotomy revealed ureteral involvement by the endometriosis. Thus complaint of hematuria in the female patient may be the first indication of urinary tract involvement of endometriosis.

DR. ENRIQUE C. M. DECASTRO, Portland, Oregon. Dr. Moore says "curiously the ovary was not involved" in one of his cases of endometriosis involving the uterosacral ligaments. It has been our observation that many times we do find that when the uterosacral ligaments are involved early in the course of the disease the ovaries are free of disease. I wonder in these situations whether one would consider conserving the ovary. I do feel that there are different etiologies in endometriosis. In those cases involving the uterosacral ligaments (retrograde menstruation theory) many times we will find the ovaries completely free of disease. In the past, we have all felt that complete removal of the ovaries is a necessity, but I am beginning to wonder if there are not instances where this could be avoided.

DR. MOORE (Closing). Dr. Langmade, I agree that the preferred management of patients with endometriotic obstruction or compression of the ureters is to ablate the ovaries, to remove the uterus, and to maintain the patient on a regimen of oral estrogens. I am not sure, in my own mind, how persuasive we should be in encouraging young, nulliparous patients to have surgical ablation of the ovaries. I think somewhat as Dr. deCastro alluded to, that perhaps if you encourage better egress of the menstrual flow, if you resect all evidence of the endometriosis, and if you watch the patients carefully, they may have a few years at least to have their children. During that time, with careful surveillance, I am not sure that there is a great risk to the kidneys—although there is a risk to subsequent sur-

gery. I think these factors have to be discussed with the patient, and I feel strongly that we should not be excessively persuasive, perhaps excessively is not exactly the term, in guiding their treatment. I think they have to make that decision with a full knowledge of the risks. Dr. Langmade is right that there were two patients who were followed up for a considerable period of time when the ovaries and uterus should have been removed previously. They were observed elsewhere. One in the Phillipines (Case No. 7), who really had a horrendous history, as I think you noted, had a bowel obstruction. She later had the uterus and what was thought to be all ovarian tissue removed, but indeed the right ovary had not been completely removed and we found a corpus luteum in it at the time of resecting the persisting endometrioma for ureteral obstruction. Dr. Langmade referred to Case No. 8 and indicated that the right ureter did not seem to be too different postoperatively than it was preoperatively. You did not see it stated on the film in the slides, but it was taken 4 days postoperatively and I think there was still some edema in the field. We have since obtained a subsequent intravenous pyelogram and she has perfect drainage.

Dr. Hill, the instances of intrinsic involvement of the ureter, rather than oppression, in which the ureters were completely obstructed by the endometriosis occurred in Cases 4 and 5. Both of those lesions involved the base of the cardinal ligaments and the uterosacral ligaments and they had to be approached in the same way a radical hysterectomy is approached by entering the areas below and above the web and transecting the cardinal ligament right at the pelvic wall.

Dr. Waterman, I do not know if we can anticipate an increase in the amount of endometriosis in patients who have intrauterine contraceptive devices in place. Perhaps the device does interfere with the proper flow of menses and increase reflux, but for me it would be complete speculation and I have no evidence.

Dr. Weber, we anticipated urinary tract involvement in only four of the patients before we obtained the urinary tract studies. Then of course it became fairly obvious. In none of these instances was it a complete surprise at operation.

Dr. MacCamy, "dyschezia" means "painful defecation." It generally is associated with uterosacral ligament or cul-de-sac involvement. We did not, in any of these cases, anticipate entering the bowel. Had we so anticipated, I suppose that we would have prepared the bowel with neomycin.

Dr. deCastro, I think your point was most thoughtful. When the uterosacral ligaments are involved and not the ovaries or the peritoneal surfaces at the pelvic brim, it probably means that there has been the drippage, if you will, of menstrual reflux onto the uterosacral ligaments; at least that seems somewhat logical. I would say that when the ovaries are free of disease and the uterosacral ligaments alone are involved, perhaps we should look toward a better path of egress for the menstrual flow. As a matter of fact, Dr. Schifrin and I published an article on teenage endometriosis some 10 years ago in which this was the major thesis. In a young woman who has excruciating and incapacitating dysmenorrhea, we should look for some obstruction to menstrual flow, such as a blind uterine horn. Carrying that a little bit further, perhaps a wide dilatation of the cervix might be in order. In these young patients, who might be prone to dysmenorrhea and who demonstrate endometriosis on the uterosacral ligaments at laparoscopy, perhaps the cervix should be widely dilated. At least, one should look for a septum in the uterus that might be a cause of partial obstruction of flow. I should like to thank Dr. deCastro for bringing up that important point.

Maternal deaths associated with postpartum vulvar edema

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Reported are three maternal deaths in four patients who presented with a similar syndrome following a normal antepartum course and normal labor and delivery managed by regional or local anesthesia and midline or proctoepisiotomy. Beginning about the second postpartum day, the patients developed unilateral perineal edema and induration which progressed to generalized vulvar, vaginal, perineal, and gluteal edema and induration. These patients developed marked leukocytosis, fever, and ultimately vascular collapse; three of them died. The one patient who survived had a similar course except for vascular collapse. Unilateral vulvar induration and edema associated with fever and marked leukocytosis are ominous signs. Aggressive treatment should include the use of multiple antibiotic, crystaloid, colloid, and steroid drugs and appropriate monitoring. By this report we hope to bring attention to this rare but lethal syndrome. (AM. J. OBSTET. GYNECOL. 134:173, 1979.)

THIS REPORT concerns itself with the description of a syndrome resulting in three maternal deaths and one survival in which all patients had normal antenatal and intrapartum courses. Two or three days later the patients developed a progressive illness characterized first by the development of unilateral vulvar and perineal edema and induration. This extended next to the contralateral side and to the inner pelvis. All patients developed fever and marked leukocytosis. Ultimately all but one patient developed vascular collapse and died. Because of the striking similarity of the manifestations in each of the patients and the scarcity of reports concerning this syndrome, a report describing the findings in these patients seems warranted.

Material and results

During the period (1969 to 1976 inclusive) these patients were observed and treated, eight additional maternal deaths in 49,007 live births occurred in the County of Kern, California. Table I lists the causes of these deaths in addition to two of the three deaths comprising this report.

Table I. Maternal deaths: Kern County (1969 to 1976)*

Year	*No. of deaths*	*Cause*	*Rate/ 10,000 live births*	*No. of births in Kern County*
1969	2	Sepsis†	3.3	6,107
1970	3	Pulmonary embolism	4.7	6,339
1971	1	Angioneurotic edema†	1.6	6,147
1972	0	–	–	6,005
1973	3	Eclampsia (dead on arrival), infectious hepatitis, and pulmonary embolism	5.6	5,388
1974	0	–	–	6,109
1975	2	Fatty metamorphosis of liver, accidental death	3.1	6,374
1976	0	–	–	6,538
Total	10			49,007

*One of our patients died in Los Angeles County Hospital.
†Reported in this paper.

Table II summarizes the clinical data of the four patients comprising this report. It should be noted that

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Table II. Data on patients

Case No.	*Hospital Identification No.*	*Age (yr.)*	*Parity*	*Duration of pregnancy*	*Delivery*	*Anesthesia*	*Type of episiotomy*	*Onset of vulvar edema*	*White blood cell count (No./cu mm)*	*Onset of vascular collapse*
1	443554-1969	19	1	Term	Low forceps	Caudal plus saddle-block	Procto-episiotomy	Second postpartum day	33,000, 57,000, left shift	Fourth postpartum day
2	467908-1971	16	1	Term	Low forceps	Epidural	Midline with third-degree extension	Second postpartum day	32,500, left shift	Fourth postpartum day
3	395442-1976	24	2	Term	Spontaneous delivery	Pudendal	Midline	Third postpartum day	30,200, left shift	Fourth postpartum day
4	356516-1976	15	1	Term	Low forceps	Saddle-block	Procto-episiotomy	Third postpartum day	22,300, 27,000, left shift	None

Case No. 3 was also included in the report by Golde and Ledger.[2]

Comment

Although the microbial agents responsible for this syndrome in these women have not been identified, the clinical course represents a form of bacterial gangrene as described by Borkowf.[1] He identified two clinical courses: (1) a gas gangrene caused by *Clostridia* or a necrotizing fasciitis classically caused by anaerobic streptococcus, and (2) a less virulent form of progressive synergistic bacterial gangrene classically caused by streptococcus and pathogenic staphylococcus in combination. These are old terms and antedate the antibiotic era. Rea and Wyrick,[5] writing on necrotizing fasciitis, stated that the most significant manifestation of this infection is "extensive necrosis of the superficial fascia which results in widespread undermining of the surrounding tissue and extreme systemic toxicity regarding less of the specific bacterial etiology." The initiating injury leading to these infections was minor trauma in 80% of their cases. In many cases the trauma was located on the abdomen or extremities. None occurred in the perineal areas. Their treatment consisted of antibiotics and wide surgical debridement. Antibiotics alone did not appear to lower the mortality rate. Their mortality rate was 30% and this was mostly in those patients who had diabetes or arteriosclerosis. The average time from the onset of the disease to the initiation of therapy was 4 days among the survivors. Prominent features of each of the bacterial gangrenes are skin manifestations, usually some evidence of necrosis and often a foul "fish-water" discharge. Stone and Martin[6] described a synergistic necrotizing cellulitis. Some cases started in the perineum. These patients were almost entirely diabetic and debilitated and beyond 50 years of age. They reported a high mortality rate from these lesions because of inaccessibility and inability to debride.

Our cases are characterized by massive edema (Fig. 1) and compromised blood supply as evidence by the paucity of bleeding from cut surfaces. With the exception of the patient sent to the University of Southern California Medical Center, skin necrosis was not evident and a foul-smelling "fish-water" discharge was not present. The common histologic change found in all biopsy and autopsy sections is one of subcutaneous and soft tissue edema and inflammation beginning unilaterally in the area of the episiotomies. Edema was present not only in the vulvar tissues but also at autopsy in

X-ray and ultrasound examinations	*Fever ℃*	*Operative intervention*	*Cultures*	*Treatment*	*Outcome and comment*
Pleural effusion, obliteration of psoas shadows	39.4°	Incision and drainage of ischiorectal fossa. No abscess found. Minimal bleeding	None	Ampicillin, kanamycin, corticosteroids, chloramphenicol, crystalloids, colloids and heparin	Died sixth postpartum day. Autopsy denied
–	38.5°	Tracheotomy	Urine and blood cultures—negative. Lochia—klebsiella, aerobacter, bacteroides	Local heat, Carbenicillin, kanamycin, gentamicin, cortisone, crystalloids	Died fourth postpartum day. Autopsy findings, limited to perineal vaginal tissues, showed marked hemorrhage, inflammation, and edema
–	38.2°	1. Episiotomy opened and incision and drainage of vagina and gluteal areas. No bleeding. 2. Colostomy. Debridement of perineum. Subtotal hysterectomy	Perineum and vaginal tissues—streptococci, *Clostridium sordellii*, staphylococci (coagulase negative)	Cephalothin, chloramphenicol, gentamicin, corticosteroids, crystalloids	Died on fourth postpartum day. Histology showed subepithelial necrosis, inflammation, and necrosis of perineum
Intravenous pyelogram, sonography showed right-sided pelvic mass	37.2°	Episiotomy opened. No bleeding	Urine and blood—all negative	Penicillin, gentamicin, ampicillin, corticosteroids, crystalloids, colloids	Alive. Discharged on twenty-third postpartum day

the retroperitoneal tissues and the mesentery.

No definite etiology has been determined nor has any commonalty in medications, type of suture materials, or infectious agents emerged. Special histologic examinations for both bacteria and fungi were negative. Search for possible sources of contamination in the patients comprising this report has been nonproductive. No reports of infections from contaminated suture material have appeared in the past 10 years (Med-Line search), although many decades ago catgut clostridial infections sometimes arose from viable spores remaining in the raw materials. Such infections would have identifiable epidemiologic characteristics. A possible source of infection is the patient herself. Since each of these patients had a midline episiotomy or an extension into the anal and/or rectal area by deliberate incision (proctoepisiotomy) or spontaneously, contamination from the fecal stream is a possibility and also from anaerobic microbial organisms normally present in the vagina. Except for Case No. 3 no positive blood or tissue cultures were obtained in any of the patients. The positive cultures from the lochia have no probable significance since similar organisms can be grown from asymptomatic postpartum patients. Also organisms isolated in Case No. 3 (*Clostridium sordellii* and coagulase-negative staphylococcus) probably are not the pathogens causing the patients' state.[4]

Our patients were all healthy pregnant women with no known complicating disease. Hibbard and associates[3] reported unusual postpartum infections in women who had normal antenatal courses and normal labor and deliveries. Six of them had either subgluteal or retropsoas abscesses. These infections followed paracervical or pudendal blocks and often required surgical drainage and debridement. Likewise our patients had normal pregnancies, labors, and deliveries; the "infections" began in the episiotomies and were not purulent but were characterized by massive edema and induration of the vulvar, gluteal, and perineal areas and extended to one or both pelvic side walls (Figs. 1 to 3, Case No. 4). Ultimately intravascular volume could not be maintained and the patients died.

Golde and Ledger[2] reported three postpartum patients with vulvar edema and one patient who had a necrotizing fasciitis in an incision for cesarean section. One of their patients (Case No. 3) had features similar to those of the cases reported here. Only one of their unique patients (Case No. 1) presented with features similar to those of our cases: vaginal delivery, fourth-

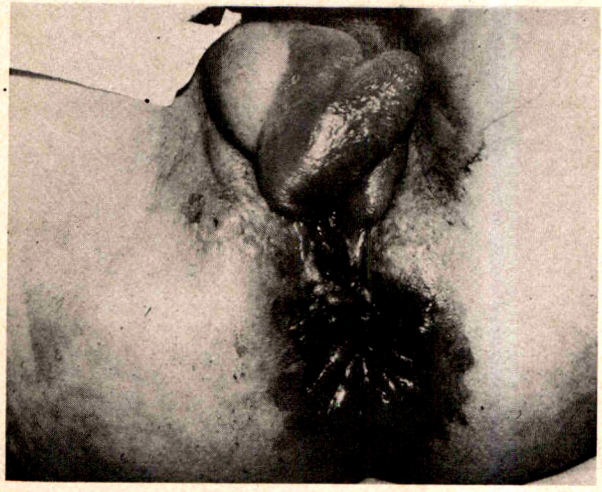


Fig. 1. Unilateral labial edema on fourth postpartum day (Case No. 4).

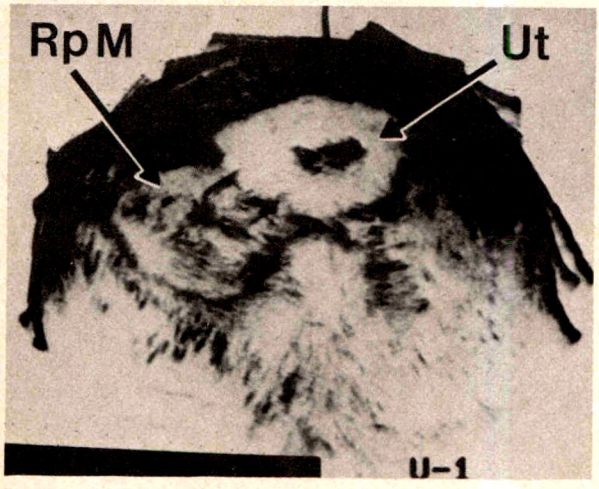


Fig. 2. Ultrasonogram showing unilateral abdominal mass *(RpM)* (Case No. 4).

degree perineal extension, and the subsequent development of a similar clinical course. Their other unique patient differed from our patients' courses in that she developed multiple abscesses of the perivaginal and retroperitoneal tissues.

From our experience we recommend early assessment of vulvar edema, particularly when it is asymmetric and occurs approximately within 48 hours after delivery. Asymmetry makes the edema distinguishable from more common causes of vulvar edema secondary to prolonged labor, etc. Temperature elevations are often of a low grade and the patient initially is reasonably asymptomatic aside from vulvar pain. The white blood cell count will most likely be greater than 20,000/cu mm with a left shift. Once the diagnosis is suspected we recommend high doses of penicillin, gentamicin, chloramphenicol, and steroids. A central venous catheter should be placed at the first sign of intravascular volume depletion and perhaps intraarterial and pulmonary wedge pressures should be monitored to guide crystalloid and colloid therapy. The anatomic location of this disease and its rapid spread up the pelvic side wall makes pelvic perineal debridement difficult and unsatisfactory. Our one surviving patient did not have tissue necrosis but cellulitis which responded slowly to the antibiotic drugs given.

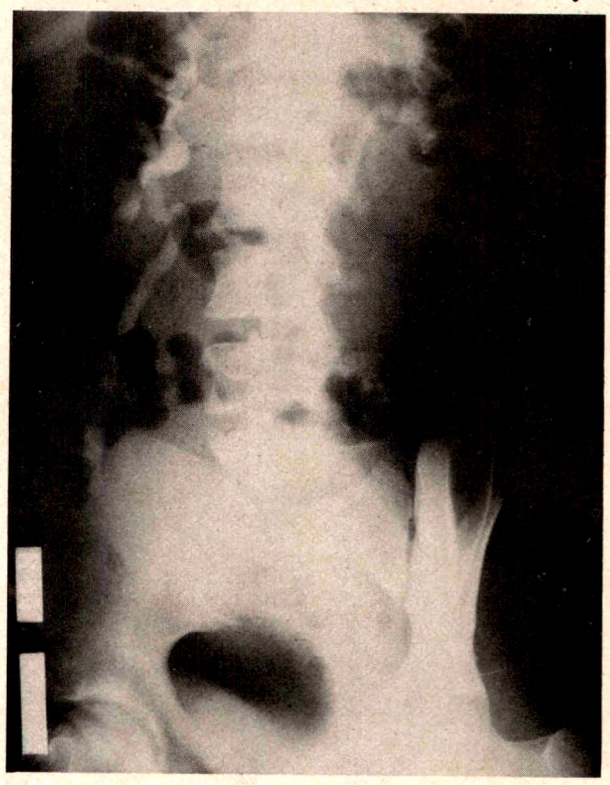


Fig. 3. Intravenous pyelogram showing deviation of ureter by mass shown in Fig. 3 (Case No. 4).

We believe this report to be pertinent because early recognition seems critical for prevention of maternal death. Aside from the report in 1977, by Golde and Ledger,[2] we have been unable to find any reports concerning vulvar edema secondary to episiotomy infection. Since only one of our patients survived, we believe also that histologic and bacteriologic study of subsequent surviving patients may shed information about an inherent idiosyncratic or immunologic deficiency that may contribute to this fatal disease.

We wish to thank Dr. Elizabeth Admiral for use of her case (Case No. 3) and Roger Terry, M.D., surgical pathologist, Los Angeles County–University of Southern California Medical Center, for his review of the tissue sections in Case No. 3.

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Discussion

DR. WILLIAM C. SCOTT, Tucson, Arizona. Acute vulvar edema is not strange to the gynecologist, occurring not uncommonly in association with trauma, infection, primary irritant dermatitis, allergic contact dermatitis, and Crohn's disease and has even been reported following paracentesis. In the vast majority of instances, however, its appearance is far from indicating a life-threatening situation. The acute hemolytic streptococcus gangrene described by Meleney,[1] in 1929, started from a superficial break in the skin and spread rapidly and alarmingly over the next 24 to 72 hours with profound prostration. The area became red, swollen, and painful with a poorly demarcated margin fading off gradually into relatively normal skin. If the process went on long enough the pathognomonic signs of dusky hew and blistering in patches developed, ending ultimately in frank gangrene. It was his belief that the rapidity and the profundity of the clinical infection suggested that the disease might be due to the entrance of organisms into the body at a time when it was in a hypersensitive state.

Following Meleney's original work the surgical literature was replete with articles describing similar syndromes later named "necrotizing fasciitis"[2] and from which a variety of organisms in addition to the hemolytic streptococcus were cultured. In addition, a necrotizing lesion of a more indolent course called "progressive bacterial synergistic gangrene" was identified.[3] Subsequent authors have reported postsurgical cases of progressive gangrene resistant to antibiotic therapy, for which they prescribed wide surgical excision, and a confusion has existed between these two diagnoses, with more recent authors feeling that they represent different facets of the same disease.[4] The first involvement of gynecology in the case reports was that of Sandusky and associates,[5] in 1942,[5] who reported 170 cases of anaerobic nonhemolytic streptococcal infection including three Bartholin's gland abscesses and one case of postsurgical salpingitis. Thirty years later Roberts and Hester[6] reported necrotizing fasciitis in six vulvar and Bartholin abscess cases. Keettel, in his discussion of their paper reported an additional Bartholin's gland abscess and two post–cesarean section cases of uterine necrosis with abdominal gangrene. Hibbard and associates,[7] in 1972, brought to our attention eight patients having uncomplicated labor and delivery, all of whom had either pericervical or pudendal block and who developed fascial and vulvar infection. One of their patients developed the typical labial edema, cellulitis, and course of necrotizing fasciitis but survived with antibiotic therapy. Bahary and associates,[4] in 1977, and Daly and associates,[8] in 1978, reported gynecologic infections with a similar course. Golde and Ledger[9] reported four cases, one of which is included in the present report, and now the present authors have added three additional cases to bring attention to this extremely serious postpartum pelvic infection with its fulminating course and high mortality rate.

Golde and Ledger, in reporting their four cases occurring during a period when there were 109,531 deliveries at Los Angeles County–University of Southern California Medical Center, emphasized by their figures the fact that this was indeed a rare condition. I would like to add to this present series a case of my own as well as to report one from Denver because I believe that despite the paucity of reports in the literature the condition is one about which every obstetrician should be concerned. To be immediately alarmed by the presence of postpartum labial edema, especially unilateral, is to be forewarned of the necessity to promptly begin antibiotic therapy with high doses of intravenous penicillin and intramuscular gentamicin and Cleocin.

A 23-year-old woman, gravida 1, para 0, with RH-positive, Type O blood, following a normal, uncomplicated pregnancy, was admitted at term with membranes intact and was delivered of a 6 pound, 5 ounce infant by spontaneous vaginal delivery following episiotomy and pudendal block on July 1, 1970. Twelve hours post partum the patient had a temperature of 99.2° F and pale vulvar edema which at that time was thought to be due to allergy to pHisoHex. The white count was 21,800/cu mm. On the second post partum day the vulvar edema was unchanged, the temperature and pulse were normal, and she was discharged. Twelve hours later she was readmitted with acute vulvar pain. On the third postpartum day the temperature was normal and the edema had spread to involve the lower abdomen and upper thigh. On the morning of the fourth postpartum day the patient had a purulent vaginal discharge from which clostridia was later cultured. Suddenly at 1200 on the fourth postpartum day the patient went into endotoxic shock. Intravenous antibiotic drugs and Solu-Cortef were started and with increasing amounts of intravenous fluids the urinary output was maintained. Despite medical management the patient went into irreversible shock and died on the fifth postpartum day. Autopsy findings revealed extreme brawny vulvar and lower abdominal edema with some degree of redness and poorly defined margins. There was retroperitoneal edema with massive amounts of fluid as well as free fluid within the abdominal and thoracic cavities. The tissue in the area of the episiotomy and ischiorectal fascia showed necrosis. The blood culture was negative and culture of tissues at autopsy was negative.

In retrospect, the prompt and early administration of large doses of antibiotic drugs at the onset of the

disease on the first postpartum day might well have prevented the ultimate death of the patient. It certainly underscores Keettel's warning, "The postpartum patient who becomes febrile and has hip or buttock pain should be suspect." An almost identical case has been reported by personal communication from Dr. Watson Bowes, occurring in St. Joseph's Hospital, Denver, Colorado. The death certificate stated "acute angioneurotic edema."

I wish to compliment the authors for bringing to our attention and through the literature to the attention of all obstetricians a rare but extremely serious complication of pregnancy. As they suggest, only prompt recognition and intensive antibiotic therapy seem at the present time to provide the decreasing mortality rates.

Drs. Ewing, Smale, and Elliott have recommended in addition high doses of steroids as soon as the diagnosis is established. As steroids have accepted value only in the presence of ligneous cellulitis and endotoxic shock and presumably could interfere with leukocytic response to this overwhelming mixed infection, I seriously question their usage in the initial phases of treatment. In their cases as well as mine antibiotic therapy was too little and too late.

Five of the six cases reviewed here were in primiparous patients, thus setting the stage for trauma in an area potentially colonized by clostridia and streptococci as well as anaerobic organisms. In the authors' cases were x-ray films obtained for gas in the pelvic tissues? Were hematomas present? And since they suggest an immunologic deficiency, what were their patients' histories of resistance to prior infection? Finally why is this complication so rare?

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Dr. Lester T. Hibbard, Los Angeles, California. I would like to add two cases to Dr. Smale's collection, both taken from the Maternal Mortality Study in California.

A 30-year-old woman, para 1, was delivered uneventfully except for a fourth-degree extension of a midline episiotomy. Thirty-six hours later, brawny edema was noted in the left labia majora and spread rapidly down both legs and up into the abdominal wall. A large loss of plasma into subcutaneous tissues was suspected on the basis of a 20 point rise in hematocrit. During the next 10 days, edema spread to involve the entire body, despite the use of steroids and muliple antibiotic drugs. Debridement was considered but rejected because of the extensiveness of the process. All cultures were negative and there was no crepitus or abscess formation. Subsequently the patient died. The autopsy diagnosis was toxic cellulitis of uncertain origin.

A 19-year-old woman, para 0, was delivered uneventfully with the aid of a left mediolateral episiotomy. On the second postoperative day, a swelling of the left labia and left buttock was noted along with chills and fever of 101° F. Triple-antibiotic therapy was begun, but the swelling increased dramatically and the patient lapsed into shock with evidence of a massive loss of plasma. The episiotomy was reopened to reveal nothing more than cellulitis from which *E. coli,* nonhemolytic streptococci, and *Clostridium perfringens* were recovered. However, there was no clinical evidence of a clostridial infection. Two treatments in a hyperbaric chamber brought temporary improvement, but the patient died before a third treatment could be started. An autopsy was inconclusive except for the demonstration of cellulitis.

Both of these patients had the benefit of multiple consultations and discussion.

Dr. John J. Molitor, Fullerton, California. The majority of patients in this series had midline episiotomies with extensions into the rectum. Most of the residents today disdain the mediolateral episiotomy and prefer the midline incision. I still think there is a place for the mediolateral incision and I use it if I think the rectum is going to be entered, because it lessens the contamination of the perineum. I have noted no difference in postoperative pain or swelling with the use of polyglycolic sutures.

Dr. Smale mentioned the elevated white blood cell counts. Several years ago, one of my colleagues was sued by a patient who developed sepsis several days after she went home following delivery. Many of our patients now go home in 24 hours. During the last 2 years, we have obtained complete blood counts on the patients the first postpartum day. We have been amazed to see that white blood cell counts of 20,000/cu mm are common. Counts of twenty-three and 23,000/cu mm and 24,000/cu mm with a marked shift to the left are frequent. So, I do not think that the white blood cell count particularly helps in the diagnosis. On the other hand, if these patients, on the first or second postpartum day, have an elevated white blood cell count it does not necessarily mean that they have infec-

tion, because most all of these patients I mentioned had no postpartum difficulties after they went home.

In my experience, unilateral edema of the vulva following delivery is usually due to hematoma in the pelvis. Frequently this has occurred where the fetal head came into close approximation with the ischial spine and a vessel was ruptured submucosally. A hematoma develops and the patients experience a great deal of pain and swelling. When the hematoma is evacuated the symptoms are relieved and the patients recover.

DR. KEITH P. RUSSELL, Los Angeles, California. I believe that not enough attention has been paid to another factor which may enter into this condition, and that is the use of local anesthesia injected in the area. We often take too much for granted that the injection of medication for pudendal or perineal block is without hazard. Some of these cases correlate with the type of reaction seen with local anesthesia or a contaminated injectable agent. It reminds me of the problem a number of years ago of infections after spinal anesthesia, which was being used frequently. A number of these cases were traced to cracks in the drug containers, with contamination of the material which was injected. I think that until this factor is at least considered we must look to this possible etiology and not assume that this is some rare clinical occurrence. We must review the material that is being injected into these tissues, which then may become severely edematous and/or infected.

DR. ROBERT H. GREGG, Covina, California. In the evolution of this most serious problem, I am interested in knowing the status of the vascular tree, both venous and arterial, as well as the status of the hemodynamics and intravascular clotting mechanism.

DR. SMALE (Closing). In most of our patients we started steroids after the patient began to lose intravascular volume, which was early in the course of the disease. We felt that these patients were developing disseminated intravascular coagulation and we were using the steroids as one of the things to hopefully "plug up" the holes in the vessels. We did obtain x-ray pictures and there was no visualized gas, and there were no hematomas. We certainly considered hematoma as one of the first things for which to search.

These were all young ladies and all were in good health. We have no idea why it is so rare, but we are glad it is such a rare disease because it is really a very lethal one in our experience. I appreciate Dr. Hibbard's contribution of the two additional case reports and his attitude, because the more information in the literature, the more important it is going to become to all of us as obstetricians and gynecologists. As far as anesthesia is concerned, only one of the four patients had any local anesthesia; the rest had epidural or saddle-block anesthesia and one received a caudal anesthetic drug.

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A study of endocrine and metabolic variables in postmenopausal women with endometrial carcinoma

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Although an underlying endocrine-metabolic disorder has been implicated as causally related to the development of endometrial carcinoma, data to support such an association are ambiguous and/or contradictory. In this prospective study of 16 consecutive nonobese postmenopausal women with endometrial carcinoma and 16 cancer-free postmenopausal women matched for age and weight, fasting values for growth hormone (GH), insulin, prolactin, follicle-stimulating hormone, luteinizing hormone, estrone (E_1), and estradiol (E_2) were measured on 3 consecutive days. Intravenous glucose tolerance, pituitary GH release in response to arginine infusion, hyperglycemia, and hypoglycemia, and insulin secretion in response to arginine infusion and to hyperglycemia were analyzed. Our data show that these endocrine-metabolic profiles were not significantly different between the cancer patients and control subjects, suggesting that the postmenopausal woman with endometrial cancer who is not obese exhibits no accountable endocrine or metabolic disorders.
(AM. J. OBSTET. GYNECOL. 134:180, 1979.)

A DOGMA IN GYNECOLOGY is the concept that endometrial adenocarcinoma is often associated with an endocrine-metabolic disorder manifested by obesity, infertility, and impaired carbohydrate tolerance. There is considerable epidemiologic evidence that obesity and infertility are risk factors in the development of endometrial cancer.[1, 2] However, there are no consistent data which support specific and reproducible abnormalities of hypothalamic, anterior pituitary, or ovarian function. Moreover the frequently cited higher incidence of diabetes in association with endometrial carcinoma remains controversial.[3, 4]

Benjamin and associates[5, 6] have observed that both hyperglycemia after oral glucose administration and insulin-induced hypoglycemia stimulate a release of growth hormone (GH) greater in patients with endometrial cancer than in control subjects. However, Brown[7] was unable to confirm this paradoxical rise of GH in response to hyperglycemia induced by oral glucose administration in endometrial cancer patients, nor was any abnormality of thyroid or adrenal function detected. However, Brown did find significantly lower plasma luteinizing hormone (LH) levels in endometrial cancer patients, leading him to suggest that insufficient LH secretion may be causally related to the frequent occurrence of ovulatory failure, decreased fertility, and prolonged unopposed estrogen stimulation of the endometrium. Benjamin and Deutsch,[8] on the other hand, found no difference in basal LH levels between endometrial cancer patients and control subjects but did find a significantly lower level of basal follicle-stimulating hormone (FSH) among the endometrial cancer patients.

This prospective study was designed to investigate carbohydrate metabolism and anterior pituitary function in a consecutive series of postmenopausel women with proved adenocarcinoma of the endometrium and to compare the results with the findings obtained in parallel studies in a group of age- and body weight–matched postmenopausal women known to be free of endometrial cancer.

Subjects and methods

Sixteen consecutive patients with adenocarcinoma of the endometrium and a control group of 16 women

From the Department of Reproductive Medicine, University of California, San Diego, School of Medicine.

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Presented by invitation at the Forty-fifth Annual Meeting of the Pacific Coast Obstetrical and Gynecological Society, Gleneden Beach, Oregon, September 26-30, 1978.

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Table I. Population characteristics

Subject	Age (yr.)	Height (inches)	Weight (pounds)	% Ideal weight	Parity	Prior estrogen therapy (yr.)
Control subjects						
A	50	63	140	118	4	1.5
B	51	66	131	102	1	
C	51	62	121	104	0	
D	52	66	140	108	1	
E	52	62	170	146	3	
F	53	64	124	101	2	
G	53	67	170	127	3	2
H	55	68	147	106	4	
I	55	63	128	108	1	
J	57	65	124	98	0	
K	58	62	134	116	1	
L	60	64	140	114	2	4
M	62	63	128	108	2	
N	64	63	134	113	0	
O	65	65	164	130	2	
P	65	65	130	103	2	
Mean(±SE)	56.4 ± 1.3	64 ± 0.5	139 ± 4.0	113 ± 3.2	1.8	
Cancer patients						
1	51	63	120	101	4	7
2	52	62	160	138	3	
3	54	63	135	113	2	2
4	54	63	105	88	1	5
5	55	65	130	103	2	6
6	55	63	130	109	1	
7	56	65	160	124	1	
8	58	64	140	114	1	
9	59	64	125	102	0	3
10	59	66	220	171	3	
11	61	65	148	117	1	16
12	62	63	93	78	1	4
13	63	66	160	127	0	
14	66	62	125	108	2	
15	67	63	132	111	2	6
16	72	65	130	103	1	
Mean(±SE)	59.0 ± 1.5	64 ± 0.3	138 ± 7.2	113 ± 5.3	1.6	

Table II. Basal metabolic and endocrine data (mean ± SE)

	K value*	Insulin (μU/ml)	GH (ng/ml)	LH (mIU/ml)	FSH (mIU/ml)	PRL (ng/ml)	E_1 (pg/ml)	E_2 (pg/ml)
Cancer (16)	1.51 ± .11	14.2 ± 1.4	2.7 ± .5	89 ± 8	64 ± 6	19.9 ± 3.0	34.2 ± 2.5	13.6 ± 1.1
Control (16)	1.42 ± .09	12.7 ± 2.3	4.2 ± .7	92 ± 14	84 ± 11	17.8 ± 1.4	42.0 ± 4.5	15.8 ± 1.1
	NS†	NS	NS	NS	NS	NS	NS	NS

*Rate of disappearance of blood glucose after 25 gm bolus intravenously (see text).
†NS = Not significant.

who were 2 years or more postmenopausal, matched for age and weight, comprised the study populations (Table I). All the cancer patients had the diagnosis established by uterine curettage. Absence of endometrial carcinoma was confirmed by curettage or endometrial biopsy in all the control subjects. Eight of the 16 cancer patients had previously received estrogen for climacteric symptoms for 1 year or more. All hormonal medications had been discontinued at least 2 weeks before the initiation of this study. In addition all studies were repeated 8 to 12 weeks following completion of treatment. Three of 16 control subjects had received prior estrogen replacement therapy, which was discontinued at least 4 weeks prior to study. The protocol was approved by the Committee on Human Experimentation and informed consent was obtained from each subject.

Each subject was studied for 3 consecutive days, at bed rest, after an overnight fast, starting at 8:00 AM, according to the following protocol:

Day 1. Rapid intravenous glucose tolerance test, with 25 gm 50% glucose injected intravenously within 2

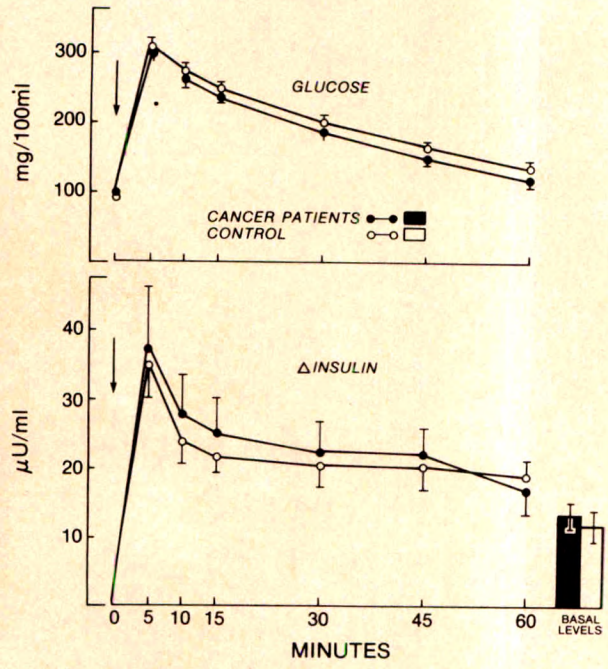


Fig. 1. Changes in plasma glucose concentration and net insulin secretion after 25 gm glucose intravenously.

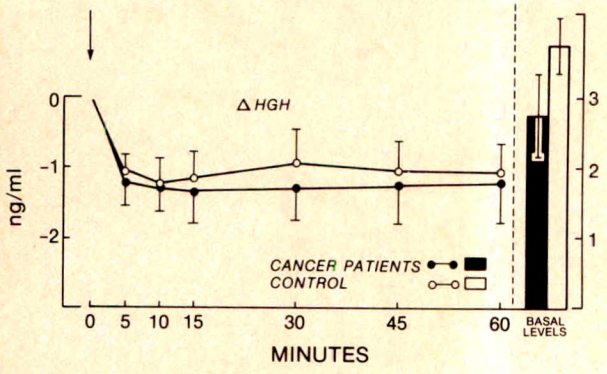


Fig. 2. Changes in GH secretion after 25 gm glucose intravenously.

minutes, and blood samples obtained at 0, 5, 10, 15, 30, 45, and 60 minutes.

Day 2. Arginine infusion, 0.5 gm/kg body weight, infused over a 30 minute period, and blood samples obtained at 0, 30, 60, 90, and 120 minutes.

Day 3. Insulin tolerance test, with 0.1 U regular insulin/kg body weight injected intravenously and blood obtained at 0, 30, 60, 90, and 120 minutes.

True plasma glucose levels were measured by Auto-Analyzer. Serum was separated and frozen at 20° C for subsequent measurement of LH, FSH, prolactin (PRL), GH, insulin, estrone (E_1), and estradiol (E_2), utilizing radioimmunoassay techniques.[9–12]

The blood glucose disappearance rate was defined as the K value, or mg/100 ml/min decline in blood glucose level following the rapid intravenous injection of 25 gm glucose. A K value of less than 1.0 indicates diabetes, 1.0 to 1.1 is considered borderline, and a value greater than 1.1 is considered normal.

Results

Baseline hormone data. The individual and the mean (±standard error) fasting plasma hormone levels on each of 3 consecutive days are shown in Table II. There were no significant differences between the cancer and control groups for any of the hormones measured.

Intravenous glucose tolerance test. The glucose response curves following 25 gm glucose given intravenously are identical in cancer patients and control subjects (Fig. 1). The mean ± standard error of the K value for the two groups is presented in Table II. Two patients in the control group and one in the cancer group had K values below 1.0, in the diabetic range. There was no significant difference between the means of the groups.

The changes in insulin and GH levels after intravenous glucose loading also show no significant differences between the two groups at any of the time periods (Figs. 1 and 2).

Arginine infusion. The fasting preinfusion levels of GH was lower in the cancer group ($p < 0.05$). However, following arginine infusion there were no significant differences in the net rise in GH or insulin levels between the cancer and control groups at all time intervals studied (Fig. 3).

Intravenous insulin. The peak hypoglycemic response to insulin (0.1 U/kg) was identical in the two groups (Fig. 4). At 90 and 120 minutes after the injection of insulin the recovery from hypoglycemia was more rapid among the control subjects ($p < 0.05$). The fasting GH level was lower in the cancer patient group ($p < 0.05$). However, there were no significant differences in the ΔGH response to hypoglycemia between the two groups (Fig. 4).

Effect of previous estrogen replacement therapy. Comparisons were made of all baseline hormone levels, response curves to arginine, hyperglycemia and hypoglycemia, and intravenous glucose tolerance between patients who had previously received exogenous estrogen therapy and those with no history of estrogen therapy. As noted, all hormonal medication had been discontinued 14 to 35 days before the initial study. In addition all 16 cancer patients were restudied for 3 days 8 to 12 weeks after completion of treatment, at which time no patient had received exogenous estrogen for over 10 weeks. No significant differences in any of the studies described above were found between the

prior estrogen therapy and no estrogen therapy groups, either (1) within the cancer patient group, (2) when all subjects who had received estrogen (N = 11) were compared with all subjects who had not received estrogen (N = 21), or (3) when cancer patients never given estrogen (N = 8) were compared to control subjects never given estrogens (N = 13). These data will be the subject of a separate report.

Correlation between baseline levels of estrogen, GH, and PRL. No correlation was found between baseline levels of E_1 and E_2 and either GH or PRL in either group (cancer group E_1 plus E_2 versus GH and versus PRL, r = 0.136 and −0.172; control group E_1 plus E_2 versus GH and versus PRL, r= 0.224 and −0.080).

Comment

Data in the literature present conflicting results with regard to most of the studies reported above.[1–8] Thus there is no uniformity of data to support carbohydrate intolerance or abnormal basal levels of any pituitary hormone or of estrogens, androgens, or adrenal corticosteroids in patients with endometrial adenocarcinoma. Controversy also exists regarding reported abnormalities of GH responses to hyperglycemia, hypoglycemia, and arginine infusion, as well as for insulin response to hyperglycemia and arginine.

The most convincing data supporting an abnormality of endocrine function are from studies of estrogen and androgen metabolism in obese patients with adenomatous endometrial hyperplasia and adenocarcinoma. There is impressive evidence that an excess of estrogen, primarily estrone, is produced via peripheral aromatization of androstenedione by obese postmenopausal women with endometrial hyperplasia or cancer.[13–19] McDonald and colleagues[13] indicate that obesity is the common denominator, since conversion of androstenedione to estrone is elevated in obese postmenopausal women whether or not endometrial hyperplasia or neoplasia exists.

In the present study all subjects were at least 2 years postmenopausal, with a mean age equivalent to the mean age reported in most epidemiologic studies of endometrial cancer.[1, 2] Obesity was not a significant feature in this group of patients. In fact the modest mean excess of weight over "ideal" weight (computed using Metropolitan Life Insurance Company height-weight tables) is compatible with the norm for a postmenopausal middle-income female Caucasian population in the United States. The results, therefore, are a comparison of the specified endocrine and metabolic indices in a well-defined patient and control population where obesity was not a significant factor.

Within this context, the striking finding is the simi-

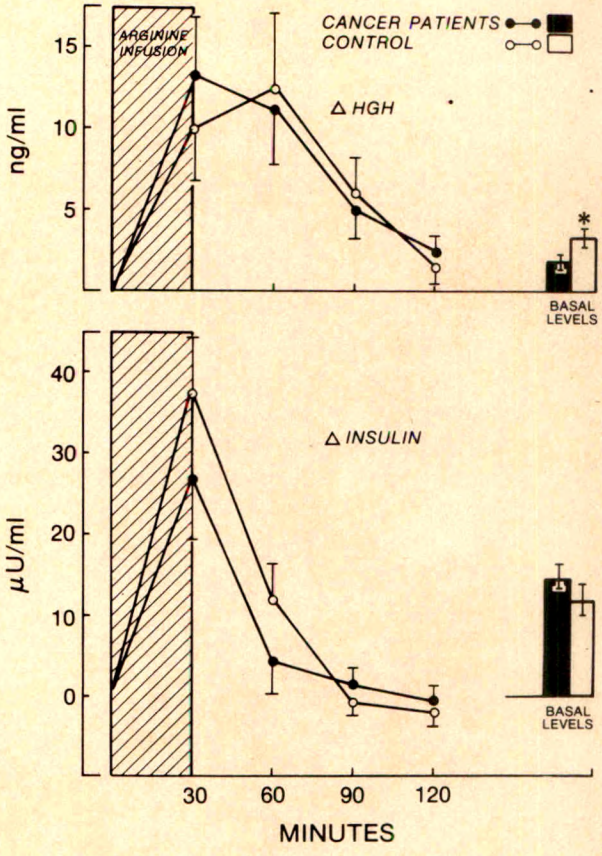


Fig. 3. Net changes in GH and insulin secretion after arginine infusion (0.5 gm/kg body weight).

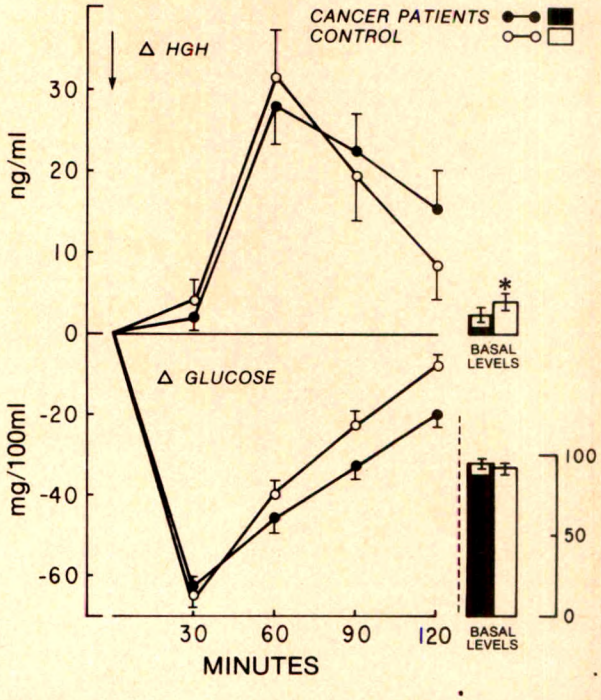


Fig. 4. Net changes in GH secretion and plasma glucose concentration after intravenous insulin (0.1 U/kg body weight).

larity of all the baseline hormone levels. In addition, hyperglycemia-, hypoglycemia-, and arginine-induced changes in GH secretion and hyperglycemia- and arginine-stimulated changes in insulin secretion were comparable between the two groups of subjects.

This study fails to support observations that abnormal GH secretion occurs in response to hyperglycemia or hypoglycemia in postmenopausal endometrial cancer patients.[5, 6]

Brown[7] reported that circulating and urinary LH levels were lower in endometrial cancer patients than in control subjects. Concomitant measurements of FSH or estrogen levels were not performed. It is inappropriate to assign any pathophysiologic significance to low LH values found in cancer patients unless the aforementioned interrelated hormones are analyzed together.[20] Nonetheless, neither observation, that baseline LH levels are significantly lower in endometrial cancer patients than in control subjects[7] or that FSH levels are significantly lower in endometrial cancer patients,[8] is supported by our data.

The similarity of serum E_1 and E_2 levels between cancer and control subjects corroborates the findings of Rader and associates[21] and a previous report from this laboratory.[22]

There was no alteration in insulin sensitivity (Fig. 3) and no increase in carbohydrate intolerance, as measured by insulin-induced hypoglycemia and a standard intravenous glucose loading technique, in the cancer patients. In fact, using a K value of less than 1 as the criterion of diabetes, three of the control subjects and only one of the cancer patients were diabetic.

An absence of any demonstrable effect of prior estrogen replacement therapy (0.625 to 1.25 mg of conjugated estrogens daily) on carbohydrate tolerance or fasting hormone levels was noted. Spellacy and associates[23] could find no effect of 1.25 mg of Premarin daily for 1 year on plasma insulin, GH, or triglyceride levels. They did note, however, an elevation of blood glucose at 1 hour during an oral glucose tolerance test compared to the preestrogen test. Hammond and associates,[24] in a retrospective comparison of 301 women on a regimen of estrogen replacement therapy for ovarian failure of a variety of causes with a matched group not receiving estrogen found no difference in the occurrence rate of any endocrine disorder during the 5 year study period. In fact, there was a lower occurrence rate of diabetes in the estrogen-treated group during the study period.

In conclusion, rather than supporting the existence of disorders of hypothalamic-pituitary function in patients with endometrial adenocarcinoma, this study suggests an absence of significant deviations from the usual postmenopausal endocrine state. We are left with the statement made by Wynder and co-workers[2] over a decade ago that "It is apparent that the primary problem of the endometrial cancer patient is obesity."

Even though the obesity-related "unopposed estrogen" hypothesis as an important factor in endometrial carcinogenesis is increasingly supported by convincing data,[13, 18] it fails to account for the not infrequent patient with endometrial cancer who is not obese, has borne children, and has never received estrogens. To date excess estrogen production or abnormal metabolism has not been observed in this group of "normal" postmenopausal women who develop endometrial cancer. This together with our present findings indicates a significant subgroup of patients in whom no discernible metabolic or endocrine abnormalities have been conclusively identified. The complexity of finding the cause, or causes, of a given cancer is re-emphasized.

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Discussion

DR. BOYD C. QUINT, Seattle, Washington. Dr. Lucas and his associates have contributed enormously to our limited knowledge of endocrine and metabolic changes surrounding endometrial carcinoma and related disorders. His[1] superb monograph in the *Obstetical and Gynecological Survey* in 1974 elegantly summarized the world knowledge on endometrial carcinoma at that time. If you have not reviewed it recently, I would suggest you do so. In that paper he pointed toward areas where further study might help unravel some of the mysteries surrounding this puzzling disease. This current presentation is a step in that direction.

Dr. Lucas pointed out in his introduction that there have been conflicting reports on metabolic changes and hormone levels in endometrial carcinoma. His protocol is designed to very well resolve some of these conflicts. The simultaneous gathering of hormone levels and metabolic changes make these results all the more meaningful. The lack of significant differences between the control subjects and cancer patients in *all* areas studied is surprising. Their graphic portrayal is striking, dramatic, and convincing. These results most effectively resolve the conflicting and contradictory reports he cites in the literature. At least in nonobese patients, we must look elsewhere for answers to the etiology of this enigmatic disease. The absence of differences in estrogen users and nonusers, regardless of group, I find particularly intriguing and look forward to Dr. Lucas's forthcoming report on this subject.

The other area considered most promising in the investigation of the etiology of this disease is the study of estrogen receptor sites. A number of studies have appeared on this subject in the recent literature.[2–7] Unfortunately, so far they face us with as much confusion as in previous hormonal studies. I have summarized

Table I. Estrogen receptor levels

Type of endometrium	*Evans and associates*[2]	*Pollow and associates*[3]	*Friberg and associates*[4]	*Crocker and associates*[5]	*Gurpide and associates*[6,7]
Proliferative	High, decreasing through cycle	High	Not treated in paper	Maximal at ovulation	High, decreasing through cycle
Secretory	Low	Low	Not treated in paper	Maximal at ovulation	Low
Adenomatous hyperplasia	High	–	Not treated in paper	–	High
Well-differentiated adenocarcinoma	Higher	Lower	Higher	No correlation with degree of differentiation	Moderate
Poorly differentiated adenocarcinoma	Lower	Higher	Lower	No correlation with degree of differentiation	Moderate

several of these reports in Table I. Three of four reports agree that receptor sites are high in normal proliferative endometrium and low in secretory endometrium. However, the fourth states they are maximal at ovulation. Both investigators reporting on adenomatous hyperplasia agree that levels here are high. The picture surrounding carcinoma is particularly blurred, as you can see. Two reports cite higher levels with well-differentiated tumors, approaching that of proliferative endometrium; one states the reverse, and the others take the middle ground. Hopefully, Dr. Lucas and his associates can generate the same sort of painstaking protocol to resolve these differences.

I have two questions to ask Dr. Lucas. What were the pathology reports on his patients? He makes no mention of degree of differentiation of the tumors of his cancer patients, whether or not their tumors were invasive, or if there were metastases. Second, had any patients in either group received oral progestins?

This is a most significant, sound paper in an area where clarification is sorely needed.

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Dr. Gilbert A. Webb, San Francisco, California. What were the ages at menopause in patients with carcinoma of the endometrium and in the control group? The subgroup referred to is an increasing one, at least as we have observed and I believe this was also mentioned by Smith. There is an increasing number of patients with adenocarcinoma of the endometrium who do not have hypertension and are not obese and who have had children, and I wondered if the age at menopause might be a significant factor.

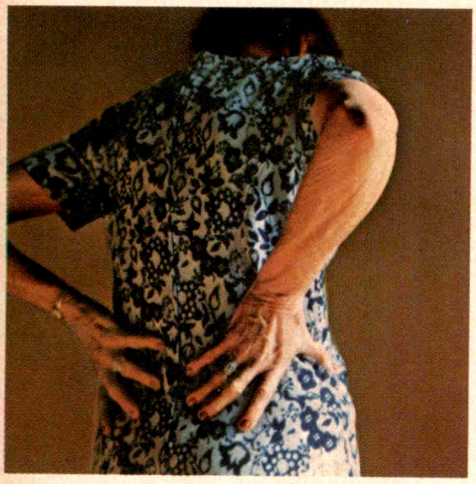
Dr. Lucas (Closing). Estrogen receptor study relative to endometrial cancer is in its infancy compared to that relative to breast cancer. Obviously, a great deal more work needs to be done in this area. By and large, one can say that there are many more similarities than differences between normal endometrium and carcinomatous endometrium, at least in its early stages, and this also is true of progesterone receptor studies. These patients all had Stage I, either A or B, adenocarcinoma of the endometrium. All had grade 1 or 2 lesions; there were no grade 3 cancers in the group. They provided the usual spectrum of pathology that one sees in a consecutive group of patients with adenocarcinoma of the endometrium. The slides in each case were re-reviewed to confirm the original diagnosis. None of these patients had received oral progestins. But I should mention parenthetically that of our 16 endometrial cancer patients, following completion of the original studies, half of the group then received high doses of Depo-Provera prior to surgery, usually during the 4 week period that they were receiving external irradiation. This did produce some interesting findings which will also be the subject of a subsequent report.

All of these patients were at least 2 years postmenopausal. I am sorry I cannot answer the question as to whether or not menopause was later compared to the overall population, but they were not as compared to the control group. As a matter of fact, the age of menopause was a little later in the control group than in the endometrial cancer group.

Postmenopausal women can lose more than estrogen...

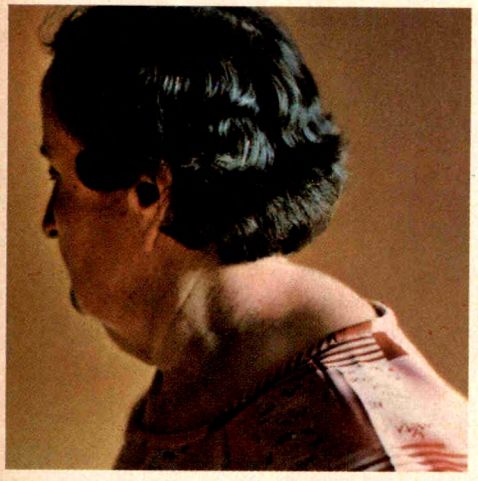


because osteoporotic bone loss* can lead to pain... muscle contracture... and other sequelae



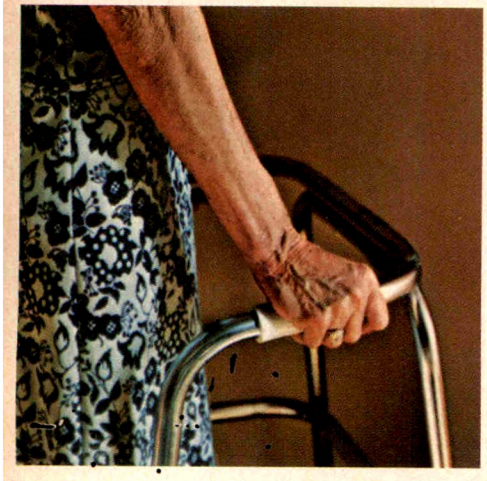
PAIN:
THE FIRST STEP IN A LONG PROGRESSION.

Postmenopausal bone loss typically progresses from "silent" symptoms to more obvious signs. Significant loss of bone tissue eventually produces thinned, weakened vertebrae that, in weight-bearing areas, may cause low back pain, typically nonradiating in nature.



THE SPINE:
A LONG-TERM TARGET.

It is not uncommon for these osteoporotic changes to lead to loss of height, with accentuated spinal curvature. In more advanced cases, the vertebrae may exhibit signs of biconcavity, collapse, and wedging.

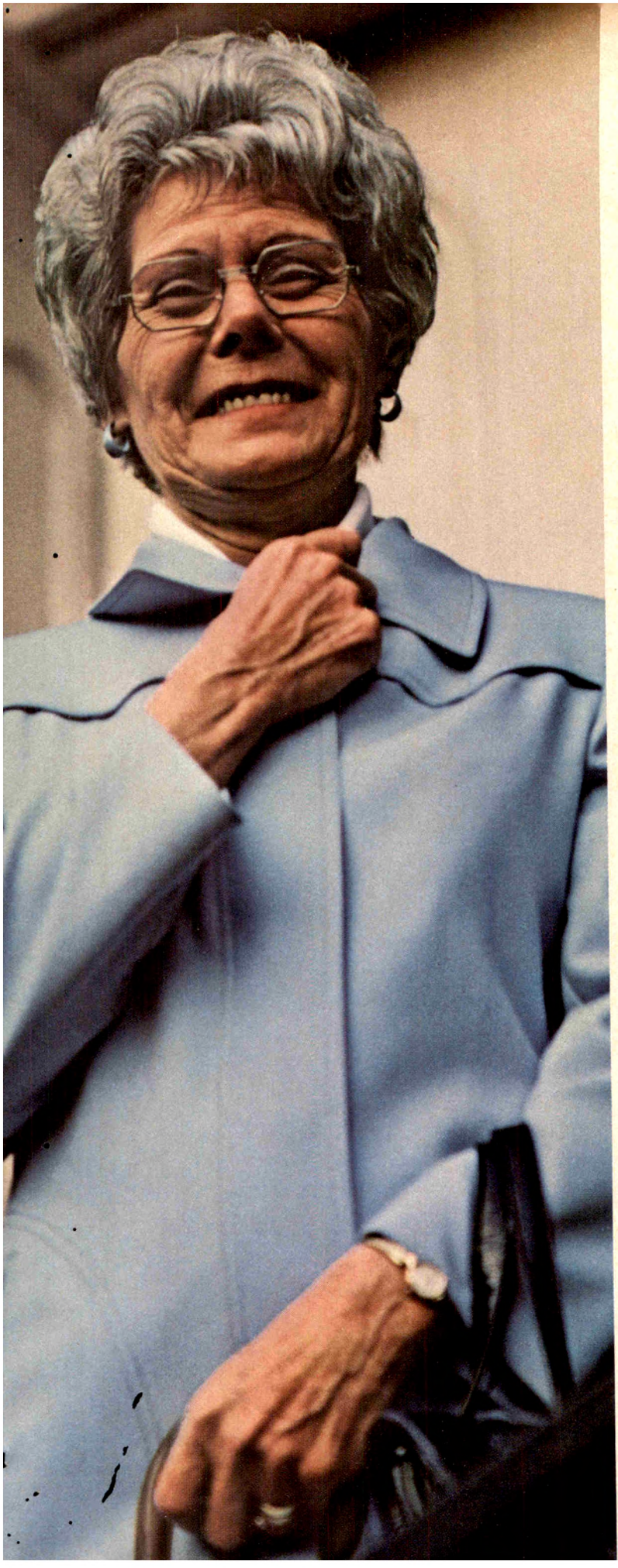


THE YOUNGER HYSTERECTOMY/ OOPHORECTOMY PATIENT— A PARTICULARLY VULNERABLE CANDIDATE.

With the prospect of prolonged estrogen deprivation and its consequences, the younger woman whose uterus and ovaries have been removed runs the greater risk of developing extensive loss of bone mass. But even if the ovaries are conserved at the time of hysterectomy, the eventual onset of natural menopause may lead to symptoms of bone loss requiring treatment.



*Conjugated Estrogens Tablets have been evaluated as probably effective for postmenopausal osteoporosis. See Prescribing Information.



effective replacement therapy should retard progression*... promote good management

Recent findings indicate that the rate of bone loss in postmenopausal women is not correlated with age but with time after menopause, and that estrogen replacement therapy significantly retards bone loss. This holds true for both the natural and the artificially induced menopause. PREMARIN (Conjugated Estrogens Tablets, U.S.P.), in conjunction with other standard measures (such as diet, calcium, and physiotherapy), can often play a significant role in retarding the loss of bone mass and minimizing such sequelae as pain, loss of height, and kyphosis.

1/ The cyclic administration of 0.625 mg or 1.25 mg of PREMARIN daily is recommended to control progression.

2/ PREMARIN should be administered cyclically even in the hysterectomized patient. Follow-up is indicated to determine a continuing need.

*Conjugated Estrogens Tablets have been evaluated as probably effective for postmenopausal osteoporosis. See Prescribing Information.

for those women who should have estrogen

PREMARIN®
(CONJUGATED ESTROGENS TABLETS, U.S.P.)
0.3mg/0.625mg/1.25mg/2.5mg

Please see next page for brief summary of prescribing information.

BRIEF SUMMARY
(FOR FULL PRESCRIBING INFORMATION AND PATIENT INFORMATION, SEE PACKAGE CIRCULAR)

PREMARIN® Brand of Conjugated Estrogens Tablets, U.S.P.

1. ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA.

Three independent case control studies have reported an increased risk of endometrial cancer in postmenopausal women exposed to exogenous estrogens for more than one year.[1-3] This risk was independent of the other known risk factors for endometrial cancer. These studies are further supported by the finding that incidence rates of endometrial cancer have increased sharply since 1969 in eight different areas of the United States with population-based cancer reporting systems, an increase which may be related to the rapidly expanding use of estrogens during the last decade.[4] The three case control studies reported that the risk of endometrial cancer in estrogen users was about 4.5 to 13.9 times greater than in nonusers. The risk appears to depend on both duration of treatment[1] and on estrogen dose.[3] In view of these findings, when estrogens are used for the treatment of menopausal symptoms, the lowest dose that will control symptoms should be utilized and medication should be discontinued as soon as possible. When prolonged treatment is medically indicated, the patient should be reassessed on at least a semiannual basis to determine the need for continued therapy. Although the evidence must be considered preliminary, one study suggests that cyclic administration of low doses of estrogen may carry less risk than continuous administration;[3] it therefore appears prudent to utilize such a regimen. Close clinical surveillance of all women taking estrogens is important. In all cases of undiagnosed persistent or recurring abnormal vaginal bleeding, adequate diagnostic measures should be undertaken to rule out malignancy. There is no evidence at present that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic doses.

2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY.

The use of female sex hormones, both estrogens and progestogens, during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a non-steroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare.[5,6] This risk has been estimated as not greater than 4 per 1000 exposures.[7] Furthermore, a high percentage of such exposed women (from 30 to 90 percent) have been found to have vaginal adenosis,[8-12] epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether they are precursors of malignancy. Although similar data are not available with the use of other estrogens, it cannot be presumed they would not induce similar changes. Several reports suggest an association between intrauterine exposure to female sex hormones and congenital anomalies, including congenital heart defects and limb-reduction defects.[13-16] One case control study[16] estimated a 4.7-fold increased risk of limb reduction defects in infants exposed in utero to sex hormones (oral contraceptives, hormone withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some of these exposures were very short and involved only a few days of treatment. The data suggest that the risk of limb reduction defects in exposed fetuses is somewhat less than 1 per 1000. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well controlled studies that progestogens are effective for these uses. If PREMARIN is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the advisability of pregnancy continuation.

DESCRIPTION: PREMARIN (Conjugated Estrogens Tablets, U.S.P.) for oral administration contains a mixture of estrogens, obtained exclusively from natural sources, blended to represent the average composition of material derived from pregnant mares' urine. It contains estrone, equilin, and 17α-dihydroequilin, together with smaller amounts of 17α-estradiol, equilenin, and 17α-dihydroequilenin as salts of their sulfate esters.

INDICATIONS: Based on a review of PREMARIN Tablets by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications for use as follows:

Effective:

1. Moderate to severe *vasomotor* symptoms associated with the menopause. (There is no evidence that estrogens are effective for nervous symptoms or depression without associated vasomotor symptoms, and they should not be used to treat such conditions.)
2. Atrophic vaginitis.
3. Kraurosis vulvae.
4. Female hypogonadism.
5. Female castration.
6. Primary ovarian failure.
7. Breast cancer (for palliation only) in appropriately selected women and men with metastatic disease.
8. Prostatic carcinoma—palliative therapy of advanced disease.
9. Postpartum breast engorgement—Although estrogens have been widely used for the prevention of postpartum breast engorgement, controlled studies have demonstrated that the incidence of significant painful engorgement in patients not receiving such hormonal therapy is low and usually responsive to appropriate analgesic or other supportive therapy. Consequently, the benefit to be derived from estrogen therapy for this indication must be carefully weighed against the potential increased risk of puerperal thromboembolism associated with the use of large doses of estrogens.[19]

PREMARIN HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING).

"Probably" effective: For estrogen deficiency-induced osteoporosis, and only when used in conjunction with other important therapeutic measures such as diet, calcium, physiotherapy, and good general health-promoting measures. Final classification of this indication requires further investigation.

CONTRAINDICATIONS: Estrogens should not be used in women (or men) with any of the following conditions: 1. Known or suspected cancer of the breast except in appropriately selected patients being treated for metastatic disease. 2. Known or suspected estrogen-dependent neoplasia. 3. Known or suspected pregnancy (See Boxed Warning). 4. Undiagnosed abnormal genital bleeding. 5. Active thrombophlebitis or thromboembolic disorders. 6. A past history of thrombophlebitis, thrombosis, or thromboembolic disorders associated with previous estrogen use (except when used in treatment of breast or prostatic malignancy).

WARNINGS: At the present time there is no satisfactory evidence that estrogens given to postmenopausal women increase the risk of cancer of the breast,[17] although a recent study has raised this possibility.[18] There is a need for caution in prescribing estrogens for women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms. A recent study has reported a 2- to 3-fold increase in the risk of surgically confirmed gallbladder disease in women receiving postmenopausal estrogens.[17]

Adverse effects of oral contraceptives may be expected at the larger doses of estrogen used to treat prostatic or breast cancer or postpartum breast engorgement; it has been shown that there is an increased risk of thrombosis in men receiving estrogens for prostatic cancer and women for postpartum breast engorgement.[19-22] Users of oral contraceptives have an increased risk of diseases, such as thrombophlebitis, pulmonary embolism, stroke, and myocardial infarction.[23-30] Cases of retinal thrombosis, mesenteric thrombosis, and optic neuritis have been reported in oral contraceptive users.[31,32] An increased risk of postsurgery thromboembolic complications has also been reported in users of oral contraceptives.[33,34] If feasible, estrogen should be discontinued at least 4 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization. Estrogens should not be used in persons with active thrombophlebitis, thromboembolic disorders, or in persons with a history of such disorders in association with estrogen use. They should be used with caution in patients with cerebral vascular or coronary artery disease. Large doses (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown[35] to increase the risk of nonfatal myocardial infarction, pulmonary embolism and thrombophlebitis. When doses of this size are used, any of the thromboembolic and thrombotic adverse effects should be considered a clear risk.

Benign hepatic adenomas should be considered in estrogen users having abdominal pain and tenderness, abdominal mass, or hypovolemic shock. Hepatocellular carcinoma has been reported in women taking estrogen-containing oral contraceptives.[36] Increased blood pressure may occur with use of estrogens in the menopause[37] and blood pressure should be monitored with estrogen use. A worsening of glucose tolerance has been observed in patients on estrogen-containing oral contraceptives. For this reason, diabetic patients should be carefully observed. Estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases.

PRECAUTIONS: Physical examination and a complete medical and family history should be taken prior to the initiation of any estrogen therapy with special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolau smear. As a general rule, estrogen should not be prescribed for longer than one year without another physical examination being performed. Conditions influenced by fluid retention such as asthma, epilepsy, migraine, and cardiac or renal dysfunction, require careful observation. Certain patients may develop manifestations of excessive estrogenic stimulation, such as abnormal or excessive uterine bleeding, mastodynia, etc. Oral contraceptives appear to be associated with an increased incidence of mental depression.[23a] Patients with a history of depression should be carefully observed. Preexisting uterine leiomyomata may increase in size during estrogen use. The pathologist should be advised of estrogen therapy when relevant specimens are submitted. If jaundice develops in any patient receiving estrogen, the medication should be discontinued while the cause is investigated. Estrogens should be used with care in patients with impaired liver function, renal insufficiency, metabolic bone diseases associated with hypercalcemia, or in young patients in whom bone growth is not complete.

The following changes may be expected with larger doses of estrogen:

a. Increased sulfobromophthalein retention.

b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.

c. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by PBI, T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered.

d. Impaired glucose tolerance.

e. Decreased pregnanediol excretion.

f. Reduced response to metyrapone test.

g. Reduced serum folate concentration.

h. Increased serum triglyceride and phospholipid concentration.

As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk.

ADVERSE REACTIONS: The following have been reported with estrogenic therapy, including oral contraceptives: breakthrough bleeding, spotting, change in menstrual flow; dysmenorrhea; premenstrual-like syndrome, amenorrhea during and after treatment; increase in size of uterine fibromyomata; vaginal candidiasis, change in cervical erosion and in degree of cervical secretion; cystitis-like syndrome; tenderness, enlargement, secretion (of breasts); nausea, vomiting, abdominal cramps, bloating; cholestatic jaundice; chloasma or melasma which may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair, hirsutism; steepening of corneal curvature; intolerance to contact lenses; headache, migraine, dizziness, mental depression, chorea; increase or decrease in weight; reduced carbohydrate tolerance; aggravation of porphyria; edema; changes in libido.

ACUTE OVERDOSAGE: May cause nausea, and withdrawal bleeding may occur in females.

DOSAGE AND ADMINISTRATION: 1. *Given cyclically for short term use only:* For treatment of moderate to severe *vasomotor* symptoms, atrophic vaginitis, or kraurosis vulvae associated with the menopause (0.3 to 1.25 mg or more daily).

The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible.

Administration should be cyclic (*e.g.*, three weeks on and one week off).

Attempts to discontinue or taper medication should be made at three to six month intervals.

2. *Given cyclically:* Female hypogonadism. Female castration. Primary ovarian failure. Osteoporosis.

Female hypogonadism—2.5 to 7.5 mg daily, in divided doses for 20 days, followed by a rest period of 10 days' duration. If bleeding does not occur by the end of this period, the same dosage schedule is repeated. The number of courses of estrogen therapy necessary to produce bleeding may vary depending on the responsiveness of the endometrium.

If bleeding occurs before the end of the 10 day period, begin a 20 day estrogen-progestin cyclic regimen with PREMARIN (Conjugated Estrogens Tablets, U.S.P.), 2.5 to 7.5 mg daily in divided doses, for 20 days. During the last five days of estrogen therapy, give an oral progestin. If bleeding occurs before this regimen is concluded, therapy is discontinued and may be resumed on the fifth day of bleeding.

Female castration and primary ovarian failure—1.25 mg daily, cyclically. Adjust upward or downward according to response of the patient. For maintenance, adjust dosage to lowest level that will provide effective control.

Osteoporosis (to retard progression)—1.25 mg daily, cyclically.

3. *Given for a few days:* Prevention of postpartum breast engorgement—3.75 mg every four hours for five doses, or 1.25 mg every four hours for five days.

4. *Given chronically:* Inoperable progressing prostatic cancer—1.25 to 2.5 mg three times daily.

Inoperable progressing breast cancer in appropriately selected men and postmenopausal women—10 mg three times daily for a period of at least three months.

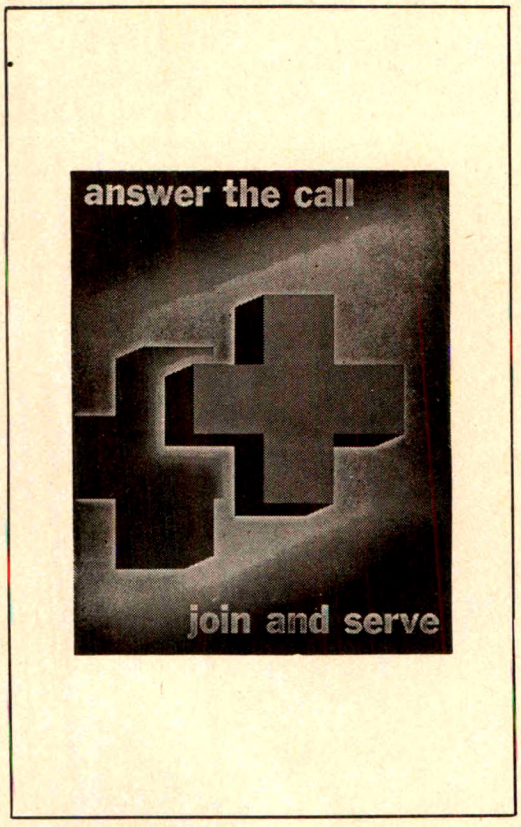
Patients with an intact uterus should be monitored for signs of endometrial cancer and appropriate measures taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

HOW SUPPLIED: PREMARIN (Conjugated Estrogens Tablets, U.S.P.) No. 865—Each *purple* tablet contains 2.5 mg in bottles of 100 and 1,000. No. 866—Each *yellow* tablet contains 1.25 mg in bottles of 100 and 1,000. Also in unit dose package of 100. No. 867—Each *red* tablet contains 0.625 mg in bottles of 100 and 1,000. Also in unit dose package of 100. No. 868—Each *green* tablet contains 0.3 mg in bottles of 100 and 1,000.

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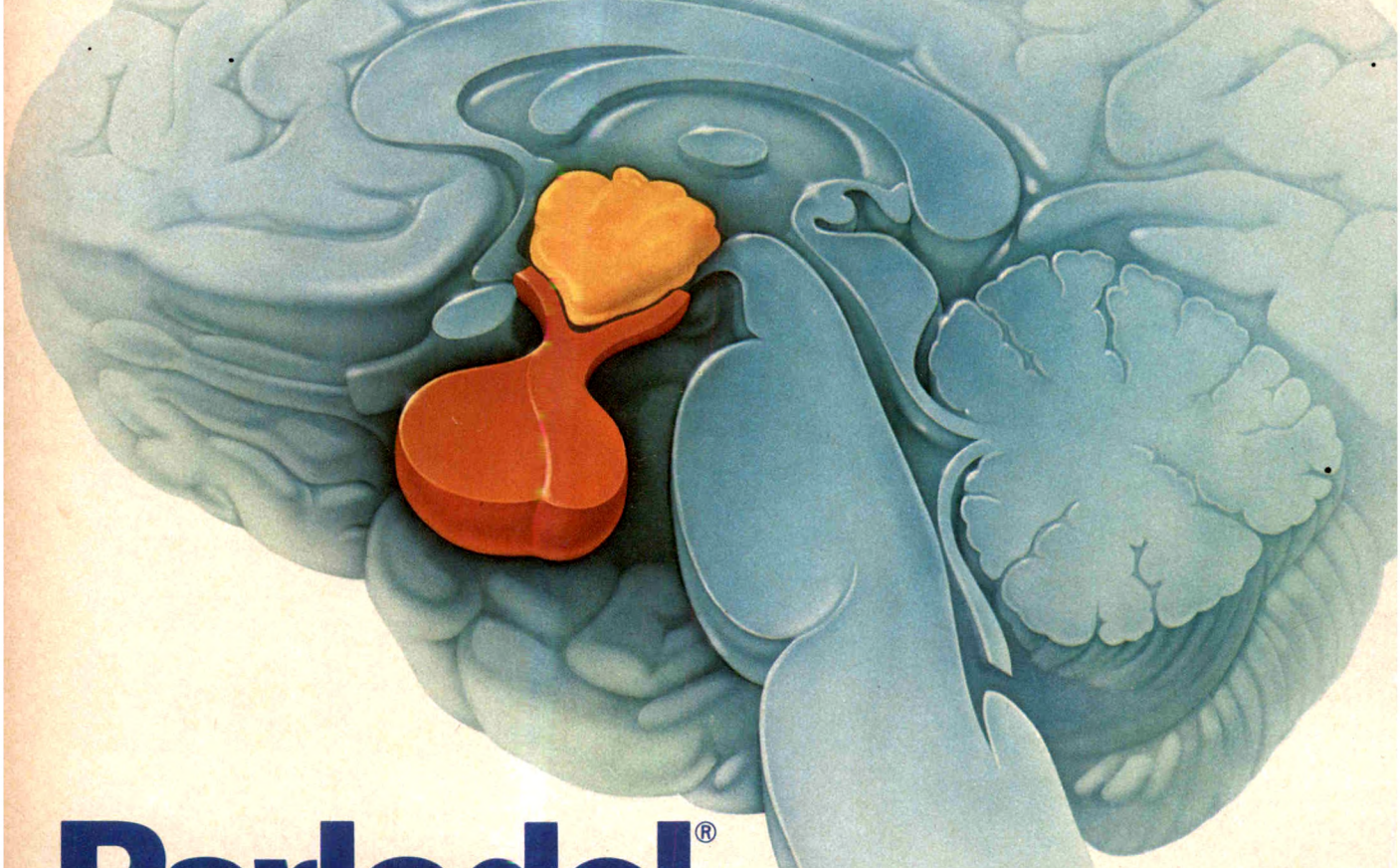
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Parlodel®
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TABLETS, 2.5 mg.

The first clinically useful dopamine receptor agonist

Dosage and Administration

- Start with one 2.5-mg tablet with the evening meal for three days; increase to one tablet with food in the morning and in the evening on the fourth day. The therapeutic dosage is one tablet two or three times daily with meals.
- If adverse effects occur, temporarily reduce dosage.
- Duration of treatment should not exceed six months.
- If pregnancy occurs, treatment should be discontinued immediately.
- For further details, including information on contraception and pregnancy tests, please see Brief Summary.

Contraindications: Sensitivity to any ergot alkaloids.
Warnings: Since hyperprolactinemia with amenorrhea/galactorrhea has been found in patients with pituitary tumors (Forbes-Albright syndrome), a complete evaluation of the sella turcica is advisable before treatment with Parlodel® (bromocriptine mesylate). Although Parlodel therapy will effectively lower plasma levels of prolactin in patients with pituitary tumors, this does not obviate the necessity of radiotherapy or surgical procedures where appropriate. If pregnancy occurs, treatment should be discontinued immediately; safe use has not been demonstrated in pregnancy. Should not be administered to nursing mothers. Safety and efficacy have not been established in children under age 15. Although the incidence of congenital malformations and spontaneous abortions reported in human studies does not exceed that generally reported for such occurrences in the population at large, the total numbe

- mimics the action of dopamine at the receptor sites
- potent inhibitor of prolactin secretion
- indicated in amenorrhea/galactorrhea associated with hyperprolactinemia*

Clinical effectiveness in amenorrhea/galactorrhea associated with hyperprolactinemia*

Parlodel therapy was studied in 210 patients with amenorrhea/galactorrhea associated with hyperprolactinemia;* of whom 187 were evaluated for efficacy. In light of the usual findings with previously available therapies, the response to Parlodel® (bromocriptine mesylate) was impressive.

- **CLINICAL IMPROVEMENT IN AMENORRHEA**
  Reinitiation of menses (or pregnancy without first having menses†) was reported by 80% of 187 patients after an average treatment time of 5.7 weeks.

- **CLINICAL IMPROVEMENT IN GALACTORRHEA**
  76% of 187 patients experienced clinically significant—75% or greater—reduction in galactorrhea, and 58% experienced complete cessation of milk secretion. The treatment time required for 75% reduction was 6.4 weeks, and that for complete cessation was 12.7 weeks.

- **OVERALL CLINICAL EFFECTIVENESS**
  63% of 187 patients experienced reinitiation of menses and at least 75% reduction in galactorrhea; 47% had both reinitiation of menses and complete cessation of milk secretion.

- **CORRELATION OF CLINICAL RESPONSE WITH REDUCTION IN PROLACTIN LEVELS**
  Improvement markedly correlated with reduction in serum prolactin levels. Maximum reduction of prolactin levels was achieved within the first four weeks of therapy, and reduced levels were maintained throughout therapy.

***in the absence of demonstrable pituitary tumor. Not indicated in patients with normal prolactin levels. Safe use in pregnancy not demonstrated. Thus, not indicated in the management of infertility.**
†Parlodel (bromocriptine mesylate) is not indicated in the management of infertility.



Stylized rendition of the hypothalamus and the pituitary

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of pregnancies reported is an insufficient sample in which to detect any given birth defect; extrapolation of these data to a greater patient population would be statistically invalid.
Precautions: Since treatment may result in restoration of fertility, patients should be required to use contraceptive measures, other than the oral contraceptives, during treatment; however, since patients often ignore this recommendation and since pregnancy may occur prior to reinitiation of menses, as an additional precaution, a pregnancy test is recommended at least every four weeks during the amenorrheic period and, once menses are reinitiated, every time a patient misses a menstrual period. Parlodel® (bromocriptine mesylate) therapy has been demonstrated to be effective in the short-term management of amenorrhea/galactorrhea only. Data are not available on the safety or effectiveness of its use in long-term continuous dosage, or in patients given repeated courses of treatment following recurrence of amenorrhea/galactorrhea after initial treatment. Recurrence rates are reportedly very high, ranging from 70% to 80% in domestic and foreign studies.
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1. Caraway, A.F.: Florida's Experience with an Intrauterine Device for the Nulliparous Patient. Presented at the International Family Planning Research Association Meeting, Palm Springs, California, October 21, 1974.
2. Caraway, A.F. and Vaughn, B.J.: J. Reprod. Med. *10*:170, April 1973.

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Medical Removal	15.6 (4.8-18.7)	23.2 (9.0-27.0)
Continuation Rate	70.4 (55.2-88.0)	59.8 (57.0-81.5)

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Health care: An enigma

ERVIN E. NICHOLS, M.D.
Washington, D. C.

IN THIS YEAR 1978, American medicine has reached goals seen unobtainable 40 years ago. The perinatal mortality rate continues to decline, death from carcinoma of the uterus is less frequent, and our female population is living longer. Yet medicine and, particularly, the discipline of obstetrics and gynecology are under ever-increasing attack.

The federal government is moving decisively in many areas relating to the practice of obstetrics and gynecology and is threatening further action in areas that have traditionally been under the direction of the profession. These actions have a direct effect on how physicians will practice their profession.

The Department of Health, Education, and Welfare has directly promulgated regulations that restrict a physician's actions in relation to sterilization and abortion.

An agency of the Department of Health, Education, and Welfare, the Food and Drug Administration, impacts on the practice of obstetrics and gynecology by inserting itself between the patient and her physician with the introduction of mandatory patient package inserts. In changing the labeling on oxytocin, this same agency has directly become involved in the setting of criteria for the practice of obstetrics and gynecology.

The use of pelvimetry, sonography, and mammography is currently being studied and evaluated by several governmental agencies—the Office of Environmental Health, the Bureau of Radiological Health, and the National Cancer Institute.

Controls have been placed on medicine by the Federal Trade Commission. By forcing consent decrees, some state medical associations and national specialty associations have had to withdraw relative value studies. It is ironic that at the time these actions are being pushed by the Federal Trade Commission requests are coming from the Department of Health, Education, and Welfare asking for fee schedules. Profiles are being assembled and it is predicted that all fees will be in a schedule in the near future.

During this same period of time, the legislative bodies of the federal government have also been active in appraising the practice of obstetrics and gynecology. One of the most important committees in the Senate has invested many hours of (nonmedical) staff time and a day in hearings assessing various aspects of obstetric practice—drugs, induction of labor, fetal monitoring, and cesarean section.

Another congressional committee has devoted much time and attention to the question of consultation prior to elective surgery with the result that there is now a section in the Department of Health, Education, and Welfare devoted solely to the planning and implementing of a program in this area.

As one looks at the activities of the various governmental bodies as they relate to health care, it becomes apparent that obstetrics and gynecology is a discipline that is heavily impacted by these actions. The question is asked why, with continuing better outcomes, are there increasing challenges to the care of obstetrics and gynecology patients by federal agencies?

This enigma (ever-better results and at the same time increasing restrictions and controls) calls for an assessment of the possible reasons why and consideration of programs for action that will maintain the forward progress in the health care of women and newborn infants.

In evaluating the reasons for legislative or regulatory actions in health care, several factors become evident. Cost is an item that transcends most actions even though often masqueraded under the guise of quality of care. Another source of activity is initiated by a small group of extremely vocal citizen activists. Mr. Nader with his Health Research Group plays a part in this scene. Health care is an issue that has strong political appeal in that it gives great visibility and provides a vulnerable target.

The activists are motivated for several reasons—some are plainly unhappy, a result of their relationship with the provider, and some have had a bad result. The

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movement for home delivery is stimulated by some of these unhappy patients. They are some of the same people pushing to change regulations to allow more professionals into the system.

The same people reputedly representing various organizations, whose constituency cannot be identified, participate in many hearings relating to the discipline of obstetrics and gynecology. They have also been influential in stimulating oversight hearings both at the legislative and administrative levels.

The last several years could be characterized as a time of cost accountability. For the past decade, Congress has increasingly passed legislation that has constantly enlarged the base of spending for health. As the base is continually broadened and the desire for tax restraint becomes more popular, someone is caught in the middle.

During this present administration, there have been ever-increasing attacks and pressures on the health providers, particularly in relation to reimbursement. Secretary of Health, Education, and Welfare Califano has continued to crusade against the present system. An ominous storm warning is the abrupt firing of Robert Derzon, Administrator of the Health Care Financing Administration. Mr. Derzon was given the task of making medicaid and medicare work. It is the opinion of many in the health field that he was a person with excellent credentials for the task assigned. Unrealistic demands for cost containment resulted in confrontation. It is reported that when congress did not pass legislation putting a cap on hospital costs, there was a push to have this done by regulation. Mr. Derzon is alleged not to have responded fast enough. The issue is cost containment versus patient care. Without a doubt the cost of delivery of health care will be a priority item for both the congress and administration in the next decade.

The problem having been posed, it seems appropriate to look at some possible remedial actions.

It is time to consider the requests of patients for changes that are not detrimental to the health of themselves or their newborn infants. An example is the consideration of providing family-centered delivery programs in the hospital setting. Community involvement in the planning of such a program can do much to reduce the barriers and tensions that are present between the provider and patient.

The incorporation of nurse-practitioners into the system will do much to fill the gap between supply and demand in special situations such as large geographic areas with small patient populations. The nurse-practitioner can function well in busy urban centers where large demands result in delayed appointments, a source of major discontent.

The target at present is cost and almost every legislative or regulatory action has cost as the primary factor or it is disguised under such terms as "quality of care," "indices for care," or "outcome audit." Cost has become the "Holy Grail" of this era. The just-launched program by the Department of Health, Education, and Welfare "second opinion" is a classic example. No matter how it is camouflaged it is an attempt at cost control. Here again is an example of government (Mr. Califano) plunging ahead with a major program without any realistic testing.

Two areas in the discipline of obstetrics and gynecology are under scrutiny, hysterectomy and cesarean section. Cesarean section is now being investigated by congressional staffs, by the Federal Trade Commission, and by agencies of the Department of Health, Education, and Welfare. There are several contracts with nonmedical groups investigating cesarean section. The reason is the rate, which then can be related to cost.

If a national cesarean section rate of 25% is appropriate then it must be justified. The best figures for 1977 put the national rate at just under 13%. Assuming a total birth number of 3 million the difference in the number of cesarean sections between 13% and 25% is 360,000. Conservative estimates say that the expenditure for a cesarean section is at least $1,000 more than the expenditure for a vaginal delivery. This then brings a new expenditure of $360 million. Congress will look at $360 million. Is the additional expenditure justified? Without a doubt it is if there are better results. It is mandatory that hard data be made available very soon. How many neonates are saved by the higher cesarean section rate? What about morbidity? Does the fetal monitor increase the rate to an abnormally high figure? Is there good evaluation by peer review? Have preset criteria been established? These questions will have to be answered and a most important paper needed today is one with hard data on the subject "justification of cesarean section in 1979."

The past 40 years have shown tremendous improvement in the care and outcome of obstetrics and gynecology patients. As techniques improve, better results can still be anticipated. Continuous re-evaluation of these techniques is a must and hard data to present to cost-conscious legislative and regulatory bodies will do much to obtain their support for good obstetric and gynecologic care.

The agencies continue to write regulations and the congress continues to enact legislation. It is a daily, ongoing process. About 18 months ago, an office was es-

tablished in Washington to serve as a liaison between the legislative and administrative branches of government and the discipline of obstetrics and gynecology. There are increasing opportunities for cooperation and increasing amounts of participation in the planning phases of legislation and regulatory programs as they relate to obstetrics and gynecology.

The discipline must provide the solid data needed to justify current and future procedures. The physician must increase his or her efforts in communicating to and educating their patients and a major program of education and advocacy must be maintained at the legislative and regulatory levels. With these actions the scales will tilt toward better patient outcome. The goal of 10 in 10 is in sight.

Discussion

DR. KEITH P. RUSSELL, Los Angeles, California. *Webster's New Collegiate Dictionary* offers the following definitions of "enigma": 1. an obscure speech or writing; 2. something hard to understand or explain. In the present instance we can discard the first definition since what Dr. Nichols is telling us is not in the least obscure. However, he does present a finding that is "hard to understand or explain": the increasing governmental incursion into the health care field, usually on the basis of invalid patchwork information, biased testimony, and, frequently, undocumented pseudoscientific observations. At all levels of government, federal, state, and local, we find this same pattern characteristic of activities involving the health care field. There are multiple examples of the classic one cited by Dr. Nichols in which one branch of government states that a relative value schedule is "price fixing" but another program administered by the government requires a fee schedule. In essence, big government says that a required fee schedule is not price fixing but that a voluntary one is.

Another classic example is that of the position of the Federal Trade Commission (FTC) in regard to certification or accreditation activities. Here are some of the questions that the FTC is asking; listen carefully as that chairman speaks:

1. Do certification and accreditation standards establish only the minimum necessary to protect the public health and safety and to prevent fraud, or do they raise an excessive entry barrier? (In other words, are you as physicians attempting to keep the total number of doctors low to create an artificial shortage, thereby improving your own economic status?)

2. Do the standards required leave room for competing models of professional function? (That is, should inferior competing models be given an opportunity to lower standards simply because they are competing models?)

3. Is the accreditation function insulated from the officers and governing body of the association? (Thus, directors or officers of the organization cannot also be examiners or evaluators.)

4. Is the accreditation function insulated from the economic and political concerns of the members? (How can it be? To exist under government requires both economic and political concerns.)

5. Are competing interests given fair representation? (If an American Association for Humanities in obstetrics and gynecology is formed we must provide fair presentation for their representatives, regardless of their qualifications.)

This sort of activity is the essence of Dr. Nichol's essay. However, he quite rightly points out that there are always two sides to the coin. Our patient population does have changing interests and changing demands, often dictated by economic as well as political considerations. I certainly agree that we as physicians must adjust and adapt to these changes. This would imply, among other things he points out, the effective use of allied health personnel and alternative birth methods under physician supervision. Such utilization has been supported by the American College of Obstetricians and Gynecologists and was emphasized a number of years ago as one of the goals of the College.

I would like to reinforce two other remedial suggestions. One is the continued and extended attempts to educate the members of congress and administration to the true facts of medical practice; the second, a more intensive approach to consideration and review of the costs which we engender for the patients we serve. A key observation is that "if organized medicine wishes to remain free from governmental regulation, it must assume responsibility for the costs it generates." There are, without question, many areas in which a concerned analysis of the costs generated could lead to a reduction in and removal of excessive costs. This often must be done on a one-to-one basis but should have the support of our organized societies.

In closing, I will mention one other aspect which is not emphasized in Dr. Nichol's essay. It is related to the continuing malpractice problem. In my opinion, one reason for a rise in cesarean section rates in many areas can be found in the professional liability implications. As anyone knows who has dealt extensively with legal activity in the obstetric field, one of the major claims which frequently reaches trial court concerns the failure to perform cesarean section in cases where there is subsequent childbirth disability. The question a defendant doctor frequently must answer is why he did not perform a cesarean section. He seldom finds himself prosecuted for performing cesarean section, unless maternal death occurs or unless there is delay in performing the cesarean section. There is little question in

my mind that this is one of the factors which contributes to an increase in cesarean section rates as we presently see them.

I have enjoyed reviewing Dr. Nichol's paper; it is a concise commentary on the present Washington scene. We are indebted to him for this Washington update on an enigma with which he is highly familiar in his position as Director of the Washington office of the College.

DR. RAYMOND J. JENNETT, Phoenix, Arizona. I think in a meeting that has, to use Howard Cosell's phrase, been replete with excellent clinical papers, this has to stand as the most important one thus far heard, as far as its significance to health care. In its presentation Dr. Nichols dealt heavily with the question of cesarean section. Dr. Russell highlighted this, I think, with one very real reason as to why there might be an increase in cesarean sections. Dr. Nichols tells us that the General Accounting Office is going to be investigating us in this regard, and the key term he used throughout his presentation was "hard data" which is a term that I think falls rather strangely on our ears because, although we are presumably a scientific discipline, "hard data" are not really part of what we like to deal with. He has stated that a group in the State of Washington has been commissioned to determine why cesarean sections are done. I had the opportunity to talk to one of the doctors of philosophy from that group who, when asked to participate in the investigation, did what any proper doctor of philosophy would do, that is, called the head of a university obstetric department and was presumably told (leaving room for hyperbole reduction) that "if I could get the 'turkeys' in my department to write down why they do c-sections, I might be able to give you an answer to that question." So if there is anything that we have to do in our industry, which we are now being reduced to or forced into doing, it is to begin to become conscious of the necessity of collecting hard data. If we do not recognize this and demand that some of our patient dollars be spent on it, we will just be playing into the hands of what has been outlined to us. As I reported to this Society last year, in Arizona we have a statewide effort to do this and by the end of this year will have 60% of all births on a uniform perinatal record system, computer based. But our grant is going to run out and so we were asked by hospital administrators, "What is it going to cost to continue this?" When we told them $2.50 per patient the reaction was that this was an excessive cost. So I think we must recognize that this is not a priority among doctors or hospital administrators and demand that it must become a high one.

DR. CARL GOETSCH, Berkeley, California. One of the enigmas to which I feel we must seek some solution is the way in which government and even some among us look at the cost of medical care and the failure to analyze what makes up the cost. Paul Ward, who is now the Executive Director of the California Hospital Association, articulates this very well when he points out that the protest against the high cost of care is against the aggregate cost of medical care without a proper analysis as to what makes the aggregate so high. He points to two particular factors which are ignored by the Department of Health, Education, and Welfare and Secretary Califano and others. One factor is the enormous explosion in technology which has created the capacity for doing very expensive but often very productive testing and remarkable procedures that are lifesaving or capable of creating a significant increase in patient comfort. There is increasing demand by our patients for these. Such things as coronary bypass surgery, which is very, very expensive and becoming extremely popular, have caused a tremendous ballooning of medical costs, whereas the substructure of the fees for usual care has increased only at the rate of rising inflation or even, sometimes, less than that. The other factor that he points to is the enormous cost that is added because of defensive practices in respect to the professional liability problem. Yet the enigma to me is that the bureaucrats are looking at our fee structures, etc., and not paying attention to what the real causes are for this ballooning of the aggregate. It is important that we, when we make our presentations, try to point this out as loudly and as clearly as we can.

DR. MAX H. PARROTT, Portland, Oregon. Dr. Nichols' comments are pertinent. I would like to point out that I gave a paper in 1966, before this organization, in Santa Barbara under a euphemistic title, "Elective hysterectomy," in which many of the same socioeconomic facts were pointed out. In those days it was quite unusual to give a so-called socioeconomic paper before this organization. I think the goals of that type of paper have been borne out here by what Dr. Nichols has had to say. In that paper I made a plea, if you can remember, that the American Medical Association and the College get together for the development of hard data relative to elective hysterectomy.

The enigma is mostly a paradox promulgated by government. These paradoxes are an administrative insistence by the bureaucratic end of government to gain and maintain control.

I have just finished 2½ years as a chairman of a national commission on the cost of medical care. It was for this reason I was late to this meeting by a day and a half. They had their final meeting on Wednesday, September 20. They now have their three volumes published. There is a lot in this document, of course, that organized medicine will not buy. However, it points out the working problems that we have with the cost issue. I hope, and I have been assured both by Dr. Nichols and by the people in the Washington office of the American Medical Association, that these people in Washington are working closely in cooperation for all of us who practice medicine. I am certain they are. I might point

out that these same problems have been going on now for the extent of my existence in organized medicine, which is some 17 or 18 years. We still do not have that great center segment of American Medicine nationalized—that is, the people who basically pay for medical care, excluding the aged, the disabled, the destitute, and the children.

Again, I think that this is a timely paper. It is a paper that deserves serious consideration and I again plead for hard data. At one time I suggested to the Committee on Gynecologic Practice of the College that they do a study on the hysterectomized public of the United States as to patient satisfaction. I am so certain that this would be favorable to us within the specialty that I would be willing to take a chance on it. I think what Dr. Nichols is really getting around to is that we have done a good job in the practice of medicine and in the specialty of obstetrics and gynecology.

What we need and what we get are two different things. We should not be confused by what is said to be in our best interest. Beware of what is being done to you under the guise of something done for you. This applies to both physicians and patients.

DR. JOHN N. MILLER, JR., Sacramento, California. There are two items in the cost that need to be brought out. They are very important. When we talk about cost control, what we are talking about is rationing of medical care and it is just a matter of who is going to do it and how, and I recommend to you an excellent article on rationing in the *Center Magazine,* July-August, 1978, from the Institute of the Center for Democratic Institutions, in Santa Barbara. I think we ought to realize what the issue of rationing medical care involves. The item of cost is put into perspective in a recent article by the President of the California Medical Association. Medical care costs $160 billion a year. I think paper work costs $100 billion a year. The public is getting quite a bargain. The other aspect that Dr. Nichols did not speak to, but I think is critical, is the courts. There is a poorly recognized arm of the courts that has a great deal to do with the regulatory body, and these are the people who are going to be involved in the Food and Drug Administration and the Federal Trade Commission and these are administrative law judges who make some very significant decisions. The government has the money to handle the repeated appeals, but I do not think the private sector has quite those resources. The last, I think, is very appropriate. I encourage you, and each of you, that we do have a monitoring office in Washington, but each of you lives in a state, and you each have state legislators and governors, etc. So I encourage you to listen to what has been said and make an effort to be informed.

DR. NICHOLS (Closing). One thing I would like to bring out in Dr. Russell's comments, and it was brought up also by Dr. Miller, has to do with liability. I would call your attention to the oversight hearings on obstetric practice. This particular item of liability was very definitively brought out and, as a matter of fact, it was introduced by Senator Schweiker as we were presenting testimony. He asked the specific question as to what percentage we thought was due to the fear of liability. They know the problem. Dr. Jennett mentioned the General Accounting Office, and I can tell you that 3 days after the Senate hearings the General Accounting Office was in our office with four people, three young lawyers and a physician, and they were gathering data on how to approach this problem. So if they have not visited you and your various institutions yet, be assured that they are "coming down the pike." To reassure Dr. Parrott, I would like him to know that the office that was established in Washington and the office of the American Medical Association do cooperate. Having said that, I can only say that we do have a job and we must get to it.

Delivery of the tiny newborn

HANNS C. HAESSLEIN, M.D.
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Obstetric factors related to the survival of 100 newborn infants weighing between 800 and 1,350 grams were analyzed. Available data suggest that maternal intrapartum antibiotic and steroid administration and delivery by classical cesarean section are associated with increased newborn survival. (AM. J. OBSTET. GYNECOL. 134:192, 1979.)

THE RECENT SUCCESS of the neonatologists in sustaining life in the tiny premature infant has presented the obstetrician with the challenge of delivering these fragile infants in optimal condition. Newborn infants weighing less than 800 grams, unless growth-retarded, have negligible survival rates. Those weighing above 1,350 grams, when managed in level III intensive care nurseries, usually do well. At the University of California, Davis (UCD) Medical Center, Sacramento, an attempt was made to follow a relatively rigid intrapartum protocol for parturients between 26 and 31 weeks of gestation who were delivered of infants weighing between this critical 800 and 1,350 gram range. Presented below are the results and a discussion of the obstetric factors relevant to these tiny infants.

Material

The population analyzed consisted of 100 infants weighing between 800 and 1,350 grams born to 83 mothers at UCD Medical Center. Thirteen women were delivered of twins and two were delivered of triplets. Ten deliveries were performed because of severe maternal toxemia and three because of signs of Stage 0 abruptio placentae. The remaining 70 patients had premature labor and/or rupture of membranes.

Method

Upon admission to the labor ward, a general history was obtained, a physical examination was performed, and an estimate was made of the duration of pregnancy. If delivery was not imminent and the estimated fetal weight was between 800 and 1,350 grams, certain routine studies were done and patients were begun on the protocol shown in Fig. 1.

An ultrasonic B-scan was obtained for estimation of fetal age and to rule out multiple gestation. An x-ray film was also obtained if there was any suggestion of fetal abnormality or abnormal fetal position. If the membranes were ruptured, amniotic fluid from the posterior fornix was obtained for a lecithin/sphingomyelin (L/S) ratio and bacterial cultures. If sufficient amniotic fluid could not be obtained or if the patient's temperature was above 38° C, an abdominal amniocentesis was performed.

When the tocolysis score[1] was 5 or less, attempts were made to inhibit labor with either: (1) a 9.5% alcohol infusion (7.5 ml/kg/hr for 2 hours, 1.5 ml/kg/hr for 10 hours) or (2) terbutaline (250 μg subcutaneously 4 to 6 hours, followed by 5 mg orally three times per day).

All patients are given a broad-spectrum antibiotic (ampicillin, cephalosporin) even if afebrile with membranes intact. Dexamethasone (12 mg intramuscularly every 12 hours, two times) was given if it appeared that delivery could be delayed for at least 24 hours. A L/S ratio was then obtained 24 hours after the last steroid injection.

A cesarean section was recommended if the fetus was in other than a vertex presentation. In two cases the cesarean section was done with the fetus in the vertex presentation solely because of inevitable premature delivery. The classical cesarean section (vertical) technique included at least a partial development of a bladder flap.

Informed consent was obtained from each woman and her husband concerning our protocols, and they were required to sign an authorization for experimental use of drugs.

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Table I. Maternal medical complications in 83 women with 100 newborn infants weighing 800 to 1,350 grams

Complication	*No.*	*%*
Premature labor	48	58
Premature rupture of membranes	22	27
Admitted in late labor	18	22
Amnionitis	12	12
Severe toxemia	9	11
Abruptio placentae > 10%	8	9
No prenatal care	8	9
Uterine anomalies	4	5
Anemia (hematocrit < 27%)	3	4
Drug addiction	1	1
Renal stones	1	1
Hyperthyroidism	1	1
Isoimmunization	1	1
Syphilis	1	1

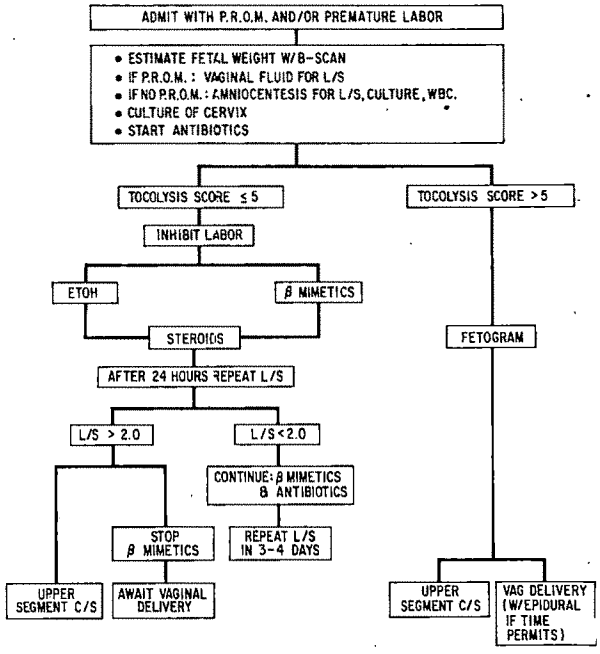


Fig. 1. Protocol for delivery of very premature infant.

Results

Twenty-two of the patients arrived in the hospital in late labor, and nothing more than delivery could be accomplished. The survival rate of the neonates in this group was 66%. After excluding patients who refused to give consent for use of our protocol or who had medical contraindications, efforts were made to inhibit labor in 58 women. In eight of these 58 patients, the decision was reversed because of suspected abruptio placentae, congenital anomalies, or revision of fetal weight estimation to more or less than the original. Admission diagnoses are listed in Table I. All 10 of the patients with severe toxemia had their pregnancies terminated by cesarean section. All of the cases of abruptio placentae were Stage 0 (i.e., no need for transfusion and no sign of fetal distress), the diagnosis being made after the delivery in five of the eight cases.

Of the 26 cesarean sections that were performed, seven were in the lower uterine segment, and 19 were in the upper segment (with four sets of twins). Twenty-seven of these 30 infants were viable, but only 23 survived. The lower uterine–segment cesarean section elicited a survival rate of only 43%. If the two fetuses with Potter's syndrome and the one stillborn infant with a prolapsed cord are excluded, the survival of the viable-size infants from the upper-segment operation is 95% (Table II) ($p < 0.05$). The mean gestational age for those delivered by cesarean section was 29.2 weeks as compared with that of the total group of 29.8 weeks. In Table II survival is analyzed according to mode of delivery. In Table III the indications for cesarean section are listed.

Seventy-two of the fetuses were delivered vaginally, including 10 of those in breech presentation, and the survival rate was 61%. The subsequent intraventricular hemorrhage rate among these newborn infants delivered vaginally was 21%, and of these only 20% survived (Table IV). The incidence of subsequent intraventricular hemorrhage was nearly twice as high in those infants delivered by low forceps as in those delivered by any other technique. One stillborn fetus had an intraventricular hemorrhage. Among the 30 fetuses delivered by cesarean section there were three intraventricular hemorrhages. Of all the neonatal deaths, 44% were associated with intraventricular hemorrhage.

Table V shows a 24% incidence of congenital anomalies. Six of these infants were delivered by cesarean section (Table V). Among the neonatal complications (Table VI), five infants had septicemia, only one of whose mother had received antibiotics prior to delivery. Infants born to mothers receiving antibiotics had a survival rate of 83%, while those not receiving antibiotics had a survival rate of 47% ($p < 0.03$).

There were only 18 newborn infants (Table VII) who had received the entire steroid protocol while in utero. Of these, 17 survived (94%) as compared with a 60% survival rate in those who had not received the entire protocol ($p < 0.10$). Of those newborn infants developing respiratory distress syndrome (RDS), the survival rate was higher when they were delivered by classical cesarean section (91%) as compared with those who had been delivered vaginally (33%).

The overall survival rate for all newborn infants weighing 800 to 1,350 grams was 65%. Postpartum maternal complications were essentially nil. Among those who had cesarean sections, three mothers were febrile without any other serious sequelae. Those mothers

Table II. Mode of delivery of 100 surviving infants

Weight (gm)	Vaginal delivery		Classical cesarean section		Low cesarean section	
	No.	% Survival	No.	% Survival	No.	% Survival
800-900	9	22	3	100	—	—
901-1,000	15	53	4	100	2	0
1,001-1,100	12	58	5	60	1	0
1,101-1,200	16	81	5	80	—	—
1,201-1,350	18	67	6	100	4	75
Total survival		61% (67%)		85% (95%*)		43% (50%)

Numbers in parentheses are corrected rates of perinatal survival.

*$p < 0.05$.

Table III. Indications for cesarean section

Indication	No. of infants	No. of surviving infants
Toxemia (severe)	10	7
Breech presentation	11*	8
Transverse lie	2	2
Abruptio placentae	1	1
Prolapsed cord	2	1
Prior cesarean section	2	2
Inevitable premature delivery	2	2
Total	30	23 (77)

*Two with renal agenesis.

with severe toxemia recovered rapidly. In one case of a woman undergoing a low transverse cesarean section for a small premature infant in a breech presentation, the cervix was lacerated as the infant was lifted from deep in the pelvis through the abdominal incision.

The following cases are presented to illustrate the problems of intrauterine infection and estimation of length of gestation in these women.

Case reports

Case 1. A 33-year-old infertility patient, para 0-1-0-0, whose membranes ruptured at the twenty-eighth week of gestation, was hospitalized elsewhere for 10 days, then transferred to UCD Medical Center because of a fever to 39° C. She was admitted to our hospital afebrile with normal laboratory findings and no labor. The estimated fetal weight was 1,100 grams, and fetal activity and a nonstress fetal heart rate test were normal. An amniocentesis recovered scant amounts of fluid which showed a white blood cell count of 4+ but no bacteria. Estriol (E_3) and human placental lactogen (hPL) levels were within normal limits.

The patient left the hospital against medical advice, but continued with broad-spectrum antibiotic therapy. Four days after leaving the hospital, she reported to her local practitioner that fetal movements had markedly decreased, but since a normal fetal heart rate was heard, she was reassured. The next day, fetal heart tones could not be heard, and she was subsequently delivered vaginally of a 1,510 gram stillborn infant from which pseudomonas was cultured.

Case 2. A 28-year-old woman, para 2-0-1-2, with a prior cesarean section for fetal macrosomia experienced rupture of the membranes at 26 weeks' gestation with the estimated fetal weight being 600 grams. The patient was placed on the protocol of steroids and antibiotics, but labor did not ensue and the patient was discharged home after a hospital stay of 6 days.

At 28 weeks, the patient was still afebrile, but the white blood cell count had risen to 23,000/cu mm. An amniocentesis demonstrated a white blood cell count of 4+ (and subsequently *Hemophilus vaginalis* was cultured). One gram of ampicillin was infused into the amniotic cavity prior to delivery. An 830 gram female infant in an incomplete breech presentation was subsequently delivered by classical cesarean section in good condition.

Although the newborn trachea and gastric fluid both showed a 4+ white blood cell count and bacteria on the smear, the cultures were negative. The mother and the infant were treated with prophylactic antibiotics and both did well.

Case 3. A 19-year-old woman, para 0-0-0-0 was referred to UCD Medical Center with a hisory of silent labor at 30 weeks' gestation. Upon admission, the cervix was 5 to 6 cm dilated, and membranes were bulging. Uterine activity was minimal and ultrasonic scan agreed with the estimated fetal age. After 3 days of bed rest, the cervix appeared to be only 2 to 3 cm dilated, and the membranes had receded. The fetal heart rate and E_3 and hPL levels were within normal limits.

An attempt at a Wurm procedure was made, but after the placement of sutures, clear amniotic fluid began to leak through the cervix. The sutures were removed, and she was continued on a regimen of ampicillin as immediate delivery was anticipated.

However, no further progress in cervical dilatation was noted over the next 15 days. Daily white blood cell counts were obtained and nonstress fetal heart rate tests were performed twice weekly. Without any changes in the white blood cell count or temperature, active labor began and she was quickly delivered of a 1,810 gram female infant in poor condition. The infant was found to have Klebsiella pneumonia and required 17 weeks of intensive care for chronic lung disease. The same Klebsiella organism was cultured post partum from the maternal cervix and uterine cavity.

Comment

Our experience suggests that the major obstetric problems surrounding the delivery of the tiny prema-

Table IV. Intraventricular hemorrhage (IVH) versus mode of delivery

Mode	*No. of infants*	*No. of survivals*	*Total No. with IVH*	*No. surviving with IVH*
Vaginal delivery (N = 70):				
Vertex, spontaneous*	37	24	8	1
Vertex, low forceps	14	9	6	2
Breech†	19	11	2	0
Cesarean section (N = 30):				
Upper segment‡	23	20	2	1
Lower segment§	7	3	1	0

*One case each of agyria, 1 multiple congenital anomalies not compatible with life, and listeria.
†One case of isoimmunization with intrauterine transfusion in twins.
‡One case of Potter's syndrome and one case of prolapsed cord with intrapartum death.
§One case of Potter's syndrome.

Table V. Anomalies of the newborn infant (N = 100)

Type	*No.*	*Delivery by cesarean section*	*Survival (%)*
Congenital anomalies	7	1	42
Patent ductus arteriosus	13	2	62
Potter's syndrome (renal agenesis)	2	2	0
Small for gestational age	3	1	100
Total	25	6	

Table VI. Complications in 100 newborn infants weighing 800 to 1,350 grams

Type	*No.*	*Survival (%)*
Intraventricular hemorrhage	19	16
Hyperbilirubinemia	17	68
Septicemia*	5	20
Newborn asphyxia	4	50
Seizures	4	25
Disseminated intravascular coagulation	3	0
Heart and renal failures	3	0

*No maternal antibiotics in four cases. $p < 0.04$.

ture newborn infant remain largely unsolved. The ultimate solution lies in the prevention of premature labor. If this cannot be done, then the major obstetric goal becomes the delivery of the tiny infant in optimal condition for subsequent development. There are several ways of solving these problems. The obstetric literature suggests that various premature labor–inhibition protocols are successful, but nearly all deal with cases of tocolysis scores lower than those described here.[3, 4]

Reports from some clinics suggest that in the absence of ruptured membranes, between 75% and 80% of the diagnoses of premature labor, in retrospect, were incorrect—the patients were not in premature labor. Others suggest that the error is as low as 30%.[4, 5] The problem of diagnosing premature labor is illustrated by Kubli's statement that in West Germany 1 million ampules and 6 million tablets of ritodrine are used annually in the prevention of premature labor in a country in which only 600,000 newborn infants are delivered per year.[4]

In this study, although only a minority of the tiny infants received the complete protocol, the data suggest that its basic concepts are valid. The benefits of steroid therapy for fetal lung maturation between 28 and 32 weeks' gestation are now proved.[7] Our prior preliminary study showed that in 20 matched cases the incidence of RDS in newborn infants weighing between 900 and 1,300 grams was reduced from 40% to 10% by the use of steroids ($p < 0.05$). Most of the neonates in the present study were delivered before the 24 hour minimum time after steroid therapy, but those who were delivered after 24 hours apparently benefited.

At the University of California, Davis Medical Center, our success with inhibition of labor is less than that generally reported in the literature[2, 3] and is about equal to that ascribed to bed rest alone. Given that steroid therapy will mature fetal lungs, even a 24 hour delay in delivery could be beneficial; however, there is general agreement that it is undesirable to deliver a tiny infant saturated with any of these tocolytic drugs. Our own lack of precision in determining when to forestall labor is illustrated by our errors in inhibiting labor in cases of unrecognized abruptio placentae or chorioamnionitis or by the opposite error of only observing a pregnant woman while she quietly and unexpectedly is delivered of a 900 gram infant.

The two controversial aspects of our protocol are the routine use of antibiotics and the frequent use of the classical cesarean section. The low-birth weight fetuses

Table VII. Effect of steroid protocol on survival by mode of delivery in 91 infants

	RDS		No RDS	
Mode of delivery	*Survived*	*Died*	*Survived*	*Died*
Infants completing steroid protocol (N = 18):*				
Vaginal delivery				
Vertex	2	1	6	—
Breech	2	—	1	—
Cesarean section				
Upper segment	2	—	3	—
Lower segment	—	—	1	—
Subtotal	6	1	11	—
Infants not completing steroid protocol (N = 76)†:				
Vaginal delivery				
Vertex	5	14	17	3
Breech	2	7	6	-
Cesarean section				
Upper segment	8	1	7	—
Lower segment	—	3	2	—
Subtotal	15	25	32	3

*Excludes one infant with severe congenital anomalies not compatible with life.

†Excludes one infant with severe congenital anomalies not compatible with life, two with renal agenesis, and two intrapartum deaths due to prolapsed cord and listeriosis.

tolerate the stress of labor less well than do the mature fetuses,[8] and less is known about the interpretation of fetal heart rate patterns of the tiny premature than about those of the mature fetus. Thus electronic monitoring offers these fetuses even less protection than it does the mature fetuses.[9] We have concluded that the severe abrupt decelerations (variable) of the FHR are often less well tolerated by these small fetuses than by the larger, mature ones.

In the absence of a well-developed lower uterine segment in the woman in premature labor, it is preferable to do a classical cesarean section, even with its immediate and remote increased risks for these patients. There is no logic in performing abdominal delivery to avoid fetal trauma and then encounter a difficult delivery through an inadequate lower-segment incision, which frequently need to be extended into a "T" incision. After nearly 40 years' experience at The Johns Hopkins Hospital, Williams[10] in 1930 recommended that the classical incision was preferred for elective cesarean section or for those women in early labor. The present reluctance to perform classical cesarean section is perhaps exaggerated, although admittedly subsequent rupture of these scars can be a rare disaster.

Steward and associates[11] found that those tiny newborn infants delivered by cesarean section did better than those delivered vaginally. In the present series only one neonate delivered by classical cesarean section died. While the findings are of borderline significance, they suggest that the tiny premature infant delivered by classical cesarean section has a better survival rate with less morbidity than those delivered by a transverse lower-segment uterine incision or vaginally. If cesarean section rates are going to be 20% or more, the small premature infant should surely benefit by this type of atraumatic delivery. This hospital's cesarean section rate of 30% for the tiny premature infant is probably too low.

Our second controversial aspect of therapy is the routine use of antibiotics, even in women with only suspected premature labor. This is based upon the concept that chorioamnionitis can be a relatively silent cause of labor. We have had, during this study, three women with Listeria and two with group B β-streptococcus whose only symptoms were premature labor and fever. In three of the five cases, the maternal fever was less than 38° C. It seems reasonable to assume that chorioamnionitis is the etiology of many cases of premature labor, even in those with intact membranes, and that antibiotics may reduce uterine activity in these circumstances.

Leukocytes in the amniotic fluid may only reflect premature labor, for approximately 20% of the amniotic fluid samples from these patients showed elevated leukocyte counts often without significant bacterial growth. When bacteria are found in amniotic fluid, amniotic cavity lavage with antibiotics is performed, and the fetus is delivered within a few hours.

The disadvantages of treating all cases of premature labor with antibiotics are that it may be a waste of medication or it may cause unnecessary sensitization to the antibiotic. Its use may also confuse bacterial study of the newborn infant. The large, multicenter study[12] frequently cited by those advocating no antibiotics for premature rupture of the membranes involved the use of a broad-spectrum antibiotic which probably did not reach the amniotic cavity in therapeutic quantities.

The case histories suggest the difficulties of preventing intrauterine infection in women with ruptured membranes. Antibiotics were obviously only partially successful, especially when used longer than 4 days, However, of the five neonates developing septicemia, four of the mothers did not receive any antibiotics. In addition to preventing neonatal illness due to susceptible organisms (streptococcus, listeria, etc.), routine antibiotic therapy may protect the newborn infant whose immunity is suppressed by steroid therapy. However, the apparent overall increased newborn survival rate with maternal antibiotic therapy is difficult to evaluate, since there was no effort made to randomize its use.

The occurrence of intraventricular hemorrhage in these small premature infants is perhaps the greatest

tragedy that can occur. The tiny premature infant is especially susceptible to this type of bleeding and its sequelae of hydrocephalus. Methods of prevention are unknown. Since the availability of computerized tomography (CT) scanners, the incidence of intraventricular hemorrhage in these infants has been found to be much higher than previously suspected.[13] Whether delivery by cesarean section will reduce the incidence of this dreadful complication is unknown at the present time. Our one case of fetal intraventricular hemorrhage prior to the onset of labor suggests that no obstetrical technique can completely prevent this newborn complication. Routine CT scanning of all tiny newborn infants may confirm our impression that the incidence of subsequent intraventricular hemorrhage is reduced by abdominal delivery.

A major problem for us has been the diagnosis of fetal anomalies incompatible with life in women in premature labor. In two cases, we antenatally diagnosed Potter's syndrome (renal agenesis) based on fetal growth retardation, absent amniotic fluid, and no urine production. Both fetuses died in utero, and while neither weighed over 1,200 grams, they demonstrated only severe growth retardation and normal genitourinary tracts. On the other hand, we have delivered by cesarean section two tiny newborn infants with Potter's syndrome following premature labor and signs of fetal distress. Increased precision with ultrasonic scanning may increase our ability to accurately diagnose these fetal anomalies.

Many of these women in premature labor must be relatively hemoconcentrated, as four of our patients, after being placed at bed rest and given intravenous fluid, have required 2 to 4 u of packed red cells in order to maintain admission hematocrits (with no clinical or laboratory evidence of blood loss). Attempts to assure normal blood volume expansion during pregnancy may be an important prophylaxis in the prevention of premature labor.

Another neglected aspect of the prevention of premature labor is the assurance of tranquility among pregnant women. Much has been written about the adverse effects of the neonatal intensive care unit on bonding and subsequent maternal-infant relationships. However, the frequent occurrence of inadequate maternal adjustments to pregnancy seen in women delivered prematurely is impressive to those dealing with this group of women. This suggests that an abnormal psychological relationship may begin between the woman and her fetus long before the onset of labor. There is little information on how the obstetrician can bring tranquility to the patient with an unwanted pregnancy, as many times the problems have no apparent practical solution.

It is obvious that the development of class III neonatal intensive care units has been a major contribution in improving the outlook for the tiny newborn infant. A recent estimate of a hospital cost of approximately $100,000 per normal suriviving newborn infant weighing 1,000 grams and less indicates the tremendous amount of expert care that the infant requires.[14] While such cases are relatively rare, obstetrics could make a significant contribution in terms of medical costs if such tiny infants could be delivered in better condition. Although our analysis is of a nonrandomized, relatively small series, it does suggest that the routine use of intrapartum steroid and antibiotic drugs, plus delivery by classical cesarean section, may make a contribution to the ultimate survival of these tiny infants. This is especially so in terms of newborn morbidity.

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Discussion

DR. LESTER T. HIBBARD, Los Angeles, California. I have enjoyed reading this thought-provoking presentation of an important clinical problem. A statistical evaluation of the data is difficult to make because premature infants are not a particularly homogenous group. This is because of the large number and variety of complications that are associated with prematurity, such as multiple gestation, obstetic hemorrhage, chorioamnionitis, breech presentation or transverse lie, toxemia, cord accident, and anomalies.

In this paper, the proposition is advanced that the survival and morbidity of infants weighing between 800 and 1,350 grams can be improved by the utilization of tocolytic agents to inhibit labor and by the addition of dexamethasone for lung maturation, prophylactic antibiotics for the prevention of chorioamnionitis, and cesarean section to reduce birth trauma, preferably by a vertical incision extending into the upper uterine segment.

In our experience at Women's Hospital, steroid therapy for lung maturation between 28 and 32 weeks substantially reduces respiratory distress and modestly reduces the perinatal mortality rate. But we still have reservations about steroids because the long-term impact on other organ systems is not known. Witness diethylstilbestrol.

We also find that chorioamnionitis is a constant problem in the management of prematurity, particularly when premature rupture of the membranes is followed by a long latent period prior to labor. Whether or not antibiotics should be used routinely is still debatable. One of the problems is to obtain precise bacteriologic information so as to be in a position to select an appropriate antibiotic. We have found that cervical cultures provide little useful information unless certain pathogens, such as gonococci or *Listeria monocytogenes,* are identified. Transabdominal cultures are more helpful, but the organisms recovered are not always the pathogens responsible for the infection. And there are hazards in the indiscriminate use of antibiotics as is illustrated by two of the authors' case examples of antibiotic therapy where an apparent superinfection resulted from the overgrowth of resistant microorganisms. One infant was stillborn with a pseudomonal infection and the other contracted disabling Klebsiella pneumonia. Our philosophy has been to treat only the obvious cases of chorioamnionitis and to withhold antibiotics in doubtful cases on the theory that the newborn infant will be better served by the ability of our neonatologists to obtain meaningful cultures prior to the initiation of therapy.

I believe that the most valuable part of the paper presented is the recommendation that abdominal delivery be employed more often and that the operation be performed in such a manner as to eliminate unnecessary operation trauma to the fetus. The key to successful management of the tiny premature infant is to ensure that the infant is born in good condition. It has been our experience that when the cervix is soft the labor proceeds rapidly without electronic or biochemical evidence of fetal distress and vaginal delivery utilizing a generous episiotomy will be sufficient. The importance of a nontraumatic vaginal delivery is illustrated by the authors' 28 infants born vaginally shortly after hospital admission of the mother with a quite respectable 66% survival rate. Where cesarean section appears to be most valuable is in those cases where premature labor begins, usually following a period of ruptured membranes, with a firm, posterior, and uneffaced cervix. If progress is slow, or there is evidence of fetal distress, an abdominal delivery greatly improves the chances for the survival of a healthy infant. The liberal utilization of a vertical incision extending as far as necessary into the upper uterine segment is far preferable to an inadequate transverse incision in a small lower uterine segment or a "T" extension of a transverse incision. I suggest that those of you who are concerned with the healing of the upper uterine segment review Potter's[1] technique for surgical repair of classical section incisions published in the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY more than 20 years ago.

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DR. JACK G. HALLATT, Los Angeles, California. We should look at the other side of the coin too. Prematurity and immaturity denote a compromised pregnancy with poor outcome and a high incidence of central nervous system deficit. Dr. Goodlin has suggested that classical cesarean section may improve this outlook; however, we still do not know the true role of method of delivery in the outcome of the immature, premature, compromised pregnancy. Prematurity itself is no threat to the health or welfare of the mother. Cesarean section is not without risk to the mother. There is a tenfold increased incidence of risk to the mother by cesarean section over vaginal delivery. There is another tenfold increased risk of uterine rupture following a classical cesarean section with a subsequent pregnancy.

This morbidity must be taken into consideration in an evaluation of the benefit-risk ratio. Should we risk the health of the mother for the possible improved salvage of this unknown quantity, the immature, premature infant? I am not quite convinced.

DR. THEODORE W. LORING, Eureka, California. I would like to mention an experience of mine which I think fits somewhat into this picture, that of a primagravid patient delivered approximately 2 years ago of a twin pregnancy. Weightwise the infants fit into Dr. Goodlin's group. However, they were born with cardiac problems and respiratory problems. They remained in our intensive care unit in Eureka for approximately 24 hours and were then transferred to Children's Hospital, in Oakland, to the intensive care unit. They remained in Oakland for approximately 3 months. Recently I was appointed to the Blue Shield Board of Directors and the Medical Director of the Board said, "You're one of those guys who has been spending our dollars on premature babies." I then looked into the matter of what happened to these two infants and found out that Blue Shield had expended approximately $225,000 in the care of these infants. Roughly $55,000 of that amount was spent on blood gas determinations. The babies are back in Eureka now; they had some atrial-septal defects and had open-heart surgery. They really are not active, healthy babies and perhaps never will be. The mother and father are deathly afraid of ever having another child. I wonder if in a situation of this nature we are doing a little bit more than necessary in attempting to save these infants who not too long ago perhaps would have died. Maybe these infants are intended to die. There was an article in the *Journal of Pediatrics* sometime ago wherein it was stated that the cost of taking care of a small premature infant to the time the baby goes home averages $200,000. I wonder, Dr. Goodlin, if you have any figures on the long-term survival and condition of these infants. You mentioned that one child is going to school and doing well. I wonder if we have any long-term figures to prove that we are doing something worthwhile.

DR. BRUCE B. ROLF, Los Angeles, California. The best way to deal with the tiny infant is to delay or prevent premature labor and birth. We must reach more of the indigent patients who account for many of the premature births. I wish to comment on extra care for the average normal patient who may also have premature labor. A pelvic examination to evaluate the cervix for early effacement at every prenatal visit may anticipate the risk of early labor. In our study, detection of effacement was treated first by insertion of a Smith-Hodge pessary and restriction of physical and sexual activity. If cervical dilatation was observed at weekly follow-up, a nylon Shirodkar cerclage and bed rest regimen as late as 28 weeks sometimes gained another 4 to 8 weeks. Barter has recommended extended bed rest after early detection of multiple pregnancy for reduction of premature births. It has been my observation that the bicornuate uterus behaves with the same relative cervical insufficiency as does multiple pregnancy. When we reviewed our cases of late cervical insufficiency, we found that a considerable number were former infertility patients who had shown an arcuate uterus on prior hysterosalpingogram. It is important for the gynecologist to review the x-ray films for configuration of the uterus as well as for tubal status. Ranney has reported on the familial trait of rapid early labors. This group also deserves frequent evaluation of the cervix for early effacement in the hope that premature labor may be delayed.

DR. RAYMOND J. JENNETT, Phoenix, Arizona. The authors have pointed out that intraventricular hemorrhage is the main threat to these tiny newborn infants. I think it should also be pointed out that Leviton and Gilles, in reviewing the collaborative project data, have shown that germinal matrix hemorrhage, a major threat to these babies, in turn is the precursor to fatal intraventricular hemorrhage, and some of the few risk factors they could identify in association with germinal matrix hemorrhage were cesarean section and hyaline membrane disease. This, in turn, should lead us back to Dr. Kimball's paper pointing out the relationship between endorphin and prolactin elaboration and the role this may have on the observed good effect of labor in the reduction of hyaline membrane disease in premature infants. Although in our department we are also aggressively following the authors' approach, that is, delivering these babies by cesarean section, we are coming up with the grim possibility that our results may not be what we had anticipated. When the outcome of these infants is compared to that of babies born in small hospitals and transported in, the latter appear to do better. This may again relate back to the matter presented in Dr. Kimball's paper. It should also stimulate Dr. Kimball to continue to gather "hard data" on this important subject.

DR. GOODLIN (Closing). It would indeed be better to have a larger sample size, but not many institutions have a large volume of tiny newborn infants. Of necessity, the study should be of short duration, for in the 25 months required to accumulate these 100 cases our techniques with ultrasound and amniotic fluid assessment improved markedly, while a preference for conduction-type anesthesia for cesarean sections has evolved and is a possible detriment.

I believe that the obstetric management of these fetuses demands as much skill as any problem that we face. It is often difficult to diagnose the presence of amnionitis, abruptio placentae, fetal anomalies, and so forth. Another concept that I have tried to "sell" is that we should abandon the technique of watchful waiting, particularly with the very tiny premature infant. A decision should probably be made either to perform a late abortion (infanticide?) or to turn to classical cesarean section when delivery seems inevitable. The condition

of many of these tiny newborn infants after vaginal delivery, if allowed to occur, is so bad that the survivors are usually afflicted with severe central nervous system problems.

In partial rebuttal to Dr. Hibbard's statement, the State Board of Health's figures for his hospital suggests that their present techniques are not optimal for normal survival of these tiny newborn infants. These figures may not be precise, but every obstetrician needs to observe the children from the intensive care nursery. I have been shocked at how badly many of the surviving tiny infants from our own unit have done.

In speaking to Dr. Hallatt's comments, I will say that we are all concerned with maternal welfare and the risk of classical cesarean section in these patients. I would suggest, however, that the occurrence of severe central nervous system problems among their children should cause us to re-evaluate the theoretical risk of cesarean section for the mothers versus the real risk of central nervous system problems in their children.

In partial answer to Dr. Loring, I was referring to the data from New Zealand which suggest that children born to mothers given steroids are doing as well in school as those who were not treated. As you know, the overall survival and performance of these children born prematurely are not as good as those of term infants. Until society accepts infanticide, we can only do our best for these tiny newborn infants to assure their optimal survival.

In answer to Dr. Jennett, I was not aware that cesarean section increased the rate of intraventricular hemorrhage in these tiny infants. My understanding was that the Arizona data suggested that it did not decrease the incidence. Only when we have a large series of these tiny infants delivered alternately by classical cesarean section versus vaginal delivery and studied by the CT scanner will we know the answer to this question. Neonatal factors seem much more important in the development of intraventricular hemorrhage, and the importance of obstetric factors may not be demonstrated unless the series is especially large.

The audience has shown skepticism in accepting the conclusion of this study, which admittedly has statistical defects. However, until a larger, better study is performed, I suggest that the present data are sufficient to begin programs of more active intervention for delivery of these tiny infants. Since their occurrence fortunately is rare, such a concept should not appreciably increase overall cesarean section rates. In the same manner that we no longer accept procrastination in prolonged labor, I believe we should not procrastinate when delivery seems inevitable for these tiny infants.

Addendum

Recently, two gravid women receiving our premature labor protocol developed apparent pulmonary edema. Extensive clinical studies suggested the cause was acute hypervolemia from mobilization of extracellular fluids (as shown by 30% decreases in hemoglobin values) plus the terbutaline therapy.

Information for authors

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Squamous carcinoma of the vulva: Results of treatment, 1938 to 1976

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Clinical data on 264 patients with squamous cell carcinoma of the vulva seen between 1938 and 1976 are reported. Two hundred and four patients were "eligible" for 5 year assessment for a 55% survival rate. Patients treated with radical vulvectomy and bilateral lymphadenectomy had a corrected 5 year survival rate of 86% if the lymph nodes failed to show metastatic disease. Twenty-eight percent of the patients treated with lymphadenectomy had lymph node metastasis at the time of surgery. The presence of lymphatic metastasis appeared to be the most significant prognostic factor. The results obtained have led to a degree of individualization in current treatment policies, together with a re-evaluation of the possible role of radiotherapy. (AM. J. OBSTET. GYNECOL. 134:201, 1979.)

CARCINOMA OF THE VULVA is the least common of the major gynecologic malignancies, ranking a distant fourth behind cancer of the cervix, ovary, and endometrium, and currently accounts for approximately 4% of all gynecologic cancers. At present, a combination of radical vulvectomy and bilateral inguinal-femoral lymphadenectomy is most often recommended[1-3] as the treatment method of choice for invasive carcinoma of the vulva. Many of the patients with this disorder are elderly and in poor medical condition, which may make selection of this treatment modality difficult and, at times, unwise.

The purpose of this paper is to review the experience obtained in the treatment of squamous carcinoma of the vulva by a variety of methods as employed at the Cancer Control Agency of British Columbia and the Vancouver General Hospital for the period 1938 to 1976 and to indicate how this experience has led to a greater degree of individualization in current treatment policies.

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Material and methods

The Cancer Control Agency of British Columbia (CCABC) and its predecessor, the British Columbia Cancer Institute (BCCI), is the major referral and treatment center for gynecologic cancer in the province of British Columbia. Although treatment policies and referral patterns have changed over the 38 years covered by this study, at present virtually all of the invasive cancers of the vulva seen in the province of British Columbia are referred to the Agency for evaluation and treatment. In the early years of the study, the initial surgical treatment was often carried out in the patient's community and patients were only referred to the Institute when recurrence or persistence of disease occurred. Although we employ radical vulvectomy and bilateral inguinal-femoral lymphadenectomy as the mainstay of treatment for squamous carcinoma of the vulva, currently we are also using combination radiotherapy and surgery for the treatment of perineal lesions involving the anal sphincter. Also, in certain instances where the patient's general medical condition was such that they were felt to be unsuitable for complete surgery, radical vulvectomy alone was done in many instances.

The charts of all patients referred to the CCABC or to the Vancouver General Hospital with the diagnosis of carcinoma of the vulva were reviewed. Patients referred with the diagnosis of melanoma, sarcoma, adenocarcinoma, or in situ carcinoma involving the vulva

Table I. Carcinoma of the vulva at CCABC, 1938 to 1976

Age range (yr.)	*No. of patients*
20-29	2
30-39	12
40-49	26
50-59	31
60-69	75
70-79	78
80-89	33
90+	7
Total	264

Table II. Presenting complaints

	Patients	
Symptom	*No.*	*%*
Mass or lesion	87	33
Pruritus	78	30
Pain or irritation	63	24
Bleeding or discharge	17	6
Not stated	14	–
Other	2	–
None	3	–
Total	264	–

Table III. Location of lesion

	Patients	
Site	*No.*	*%*
Labia majora	124	56.8
Labia minora	26	
Clitoris	40	15.0
Perineum	24	9.1
Bartholin's gland	2	–
Extensive	30	11.4
Undetermined	18	6.8
Total	264	–

were excluded from this particular study. During the interval 1938 to 1976, 264 patients were referred with a diagnosis of invasive squamous cell carcinoma.

Sixty of the 264 patients are within 5 years of follow-up and these cases were not used to compute survival statistics but were included in the assessment of presenting complaints, location of lesions, and complications.

Results

Table I shows the age distribution of the 264 patients. The youngest patient seen was 28 years of age with the oldest being 93 years. It is apparent that the disease is one of the elderly woman with disease occurring most commonly in the eighth decade (i.e., 70 to 79 years). Seventy-three percent of the patients seen were 60 years of age or older.

The presenting symptoms for the entire series are listed in Table II. A mass or lesion and pruritus noted by the patient were the two most common complaints. Pain or irritation occurred in 24% of patients, with bleeding or discharge in only 6% of individuals.

The location of the various lesions is shown in Table III. As expected, most lesions occurred on either the labia majora or the labia minora. Fifteen percent of the patients had lesions which were thought to be predominantly clitoral in origin. In 11.4%, the lesion was extensive, occupying the entire vulva, and the site of origin could not be determined. There were a further 18 patients in whom the exact site could not be determined because of insufficient data in the records.

Table IV presents the treatment method versus the stage of disease. All cases were retrospectively staged using the TNM staging system of the International Federation of Gynecology and Obstetrics. A total of 204 patients were eligible for 5 year assessment and their treatment methods, together with stage, are presented in Table V. Sixty-nine patients were treated with radical vulvectomy and superficial node dissection, superficial node dissection referring to bilateral inguinal-femoral lymphadenectomy. A further 51 patients had radical vulvectomy together with superficial and deep node dissection, deep node dissection referring to bilateral pelvic lymphadenectomy. Forty-two patients were treated with vulvectomy or wide local excision and 22 patients received radiotherapy as the only method of treatment. Five patients had radical vulvectomy in combination with an exenteration-type procedure for disease affecting the anus or bladder, as well as the vulva. Of this group, three were posterior and two were anterior exenterations.

A further seven patients were treated with a combination of surgery and various forms of radiotherapy as planned definitive treatment. This modality was used for cases where the disease was initially inoperable in an attempt to make it operable or where postoperatively disease was beyond the surgical margins. The numbers are small but the results are encouraging as five of the seven patients were alive and well at 5 years.

In eight patients, no treatment was given due to general medical condition of the individual or the patient's refusal to undergo therapy. One hundred forty-four patients had either Stage I or Stage II disease. There were seven patients in whom the data were insufficient to permit accurate staging.

Table VI presents the treatment method versus outcome for the 204 patients who were eligible for 5 year assessment. Approximately 77% of the patients treated

Table IV. Treatment method versus stage, 1938 to 1976

Treatment method	No. of patients	Stage				Unstaged
		I	II	III	IV	
Radical vulvectomy, superficial node dissection	100	46	34	14	1	5
Radical vulvectomy, superficial and deep node dissection	54	19	25	8	2	—
Vulvectomy	54	25	18	7	3	1
Radical vulvectomy and exenteration	9	2	2	5		
Radiotherapy	28	2	3	13	7	3
Radiotherapy and surgery	9	4	1	2	1	1
None	10		4	2	4	—
Total	264	98	87	51	18	10

Table V. Treatment method versus stage, 1938 to 1972

Treatment method	No. of patients	Stage				Unstaged
		I	II	III	IV	
Radical vulvectomy, superficial node dissection	69	33	24	8	1	3
Radical vulvectomy, superficial and deep node dissection	51	19	23	7	2	—
Vulvectomy	42	19	12	7	3	1
Radical vulvectomy and exenteration	5	1	2	2		
Radiotherapy	22	1	3	10	6	2
Radiotherapy and surgery	7	3	1	1	1	1
None	8		3	1	4	—
Total	204	76	68	36	17	7

with radical vulvectomy and bilateral inguinal-femoral node dissection were alive and well with no evidence of disease at 5 years. Those individuals in whom bilateral pelvic lymphadenectomy was done in addition to radical vulvectomy and superficial node dissection had a 69% 5 year survival rate. Over all, 55% of the patients were alive and free of disease at 5 years, irrespective of stage or treatment method.

The relationship of nodal involvement at the time of radical surgery to outcome is presented in Table VII. Patients who had only removal of inguinal-femoral nodes and in whom the nodes were negative had a corrected 5 year survival rate of 86%. In those individuals with positive superficial nodes, the survival rate decreased to 56%.

In patients who were treated with radical vulvectomy and inguinal-femoral and bilateral pelvic lymphadenectomy, the overall 5 year survival rate was approximately 69%. No patients were seen in whom the deep nodes were positive and the superficial nodes were negative. If all nodes were negative or if only the superficial nodes were involved, the survival data are similar to those for patients with negative inguinal-femoral nodes without pelvic lymphadenectomy. Two of four patients with pelvic disease were alive and well at 5 years. No patient with a lesion less than 2.5 cm in greatest diameter had nodal disease. The four patients with positive pelvic nodes were individuals with either clitoral lesions or extensive lesions involving the entire vulva. Twenty-five percent of the patients had bilateral nodal disease. In all, 34 (28%) of the patients who had node dissection had positive nodes at the time of surgery. This figure is low in comparison to those of other series[1, 2] in the literature and may be a reflection of inadequate histologic study of the material or earlier diagnosis and treatment as 99 of 120 patients who had node dissections had either Stage I or Stage II disease.

The overall 5 year survival results by stage are presented in Table VIII. The crude 5 year survival result for all stages was approximately 55% and when corrected for death due to other causes was 58.2%. The corrected 5 year survival rates for Stage I and II disease were 85% and 58%, respectively. Although the numbers are small, the corresponding corrected 5 year survival rate for Stage III disease was 24%.

There were 163 patients available for 10 year

Table VI. Treatment method versus outcome, 1938 to 1972

Treatment method	Total	Outcome				
		Alive and well	*Died of disease*	*Died of intercurrent disease*	*Alive with disease*	*Lost to follow-up*
Radical vulvectomy, superficial node dissection	69	53(76.8%)	11	1	1	3
Radical vulvectomy, superficial and deep node dissection	51	35(68.6%)	11	2	—	3
Vulvectomy or excision	42	14(33.3%)	15	6	6	1
Radical vulvectomy and exenteration	5	1(20.0%)	4	—	—	—
Combined surgery and radiotherapy	7	5(71.6%)	2	—	—	—
Radiotherapy	22	5(23.0%)	16	1	—	—
None	8	—	7	—	1	—
Total	204	113(55.4%)	66	10	8	7

Table VII. Status of nodes versus outcome at 5 years, 1938 to 1972

	Total	*Alive and well*		
		No.	*Percentage*	
			Crude	Corrected
Radical vulvectomy, superficial node dissection:	69	53	76.8	77.9
Negative	51	43	84.3	86
Positive	18	10	55.6	55.6
Radical vulvectomy, superficial and deep node dissection:	51	35	68.6	71.4
Negative	35	27	77.1	81.8
Positive superficial nodes	12	6	50	50
Positive superficial and deep nodes	4	2	50	50

follow-up and their results by stage are presented in Table IX. The figures in parentheses are the corresponding results for this group of patients at 5 years. In comparing the two sets of figures, it is interesting to note that very few patients died of disease beyond 5 years. However, the number of patients dying of intercurrent disease increased markedly after 5 years, as expected when one is dealing with a group of predominantly older individuals.

Table X presents the data on 20 of the 44 patients treated by vulvectomy or wide local excision. An argument is often made that patients with vulvar carcinoma, because of their relatively advanced age, should not be subjected to major radical surgical procedures as their anticipated life span is probably short. As can be seen, a significant number of patients of advanced age went on to die of intercurrent disease, in many instances 10 years or more following a diagnosis of their disorder. Analysis of these cases also indicated that in certain individuals, because of the early stage of disease, together with the particular growth characteristics of the tumor, procedures other than radical vulvectomy and lymphadenectomy may be effective in achieving control and possibly cure of disease.

Table XI presents the complications for the patients in this series. The overall complication rate was 22.4%. Six patients had more than one complication and there were two postoperative deaths in this series (0.8%). As expected, the most common postoperative complications were problems with wound healing or necrosis. Bilateral lymphedema of the lower extremities was the next most common complication. Of those patients with wound necrosis, six required additional surgical management of this complication; three underwent skin grafting and a further three had debridement and resuturing of wounds postoperatively.

Comment

Results of this study confirm the work of others[1–3] in that carcinoma of the vulva is an uncommon gynecologic malignancy occurring most often in women in the older age group. There is little doubt that radical vulvectomy and bilateral inguinal-femoral lymphadenectomy appears to be the method producing the best results in terms of survival and cure of disease of patients in this series. At present, this is our treatment method of choice in suitable individuals. The combination of radical vulvectomy and bilateral inguinal-femoral lymphadenectomy is perhaps the best cancer operation in the armamentarium of the gynecologic oncologist as it embodies all of the basic principles of a good cancer operation, i.e., en bloc resection of the primary tumor site, together with its primary lymph node drainage areas. As has been shown many times, squamous carcinoma of the vulva is a tumor which spreads predominantly by direct extension and by the lymphatics.[4–6] It has little propensity for blood-borne metastases. Nevertheless, it is our responsibility to constantly

Table VIII. Stage versus 5 year results: 204 patients

Stage	Total	Outcome				
		Alive and well	*Died of disease*	*Died of intercurrent disease*	*Alive with disease*	*Lost to follow-up*
I	75	60	6	4	2	3
II	69	39	21	2	4	3
III	36	8	22	4	1	1
IV	17	—	16	—	1	—
Unstaged	7	6	1	—	—	—
Total	204	113*	66	10	8	7

*Five-year survival rate of 55.4%. Corrected five-year survival rate of 58.2%.

Table IX. Ten-year follow-up: 163 patients

Stage	Total	Outcome				
		Alive and well	*Died of intercurrent disease*	*Died of disease*	*Alive with disease*	*Lost to follow-up*
I	57	34(44*)	12(4)	7(4)	(2)	4(3)
II	56	21(31)	13(3)	19(17)	1(3)	2(2)
III	31	3(6)	6(3)	21(21)	—	1(1)
IV	13	—	—	13(13)	—	—
Unstaged	6	4(5)	1(0)	1(1)	—	—
Total	163	62†(86)	32	61	1	7

*Figures in parentheses are corresponding results at 5 years.
†Ten-year survival rate of 38%. Corrected ten-year survival rate of 47.3%.

Table X. Vulvectomy only

Age (yr.)	*Outcome*	*Years*
80	D.I.	13
73	D.I.	6
73	D.I.	4
70	D.I.	18
76	D.I.	13
66	D.I.	14
63	D.I.	7
72	D.I.	6
45	D.I.	24
81	D.I.	5
84	D.I.	10
76	D.I.	4
51	D.I.	12
79	D.I.	3.5
59	D.I.	13
77	Alive and well	11
71	Alive and well	16
51	Recurrence	15
74	Recurrence	8
87	Recurrence	1 and 5

D.I.: Died of intercurrent disease.

Table XI. Complications of therapy

Complication	*No. of patients (254 patients)*
Wound necrosis	37
Leg edema	12
Serous collection	4
Wound infection	8
Stress incontinence	2
Rupture of femoral artery	1
Sexual dysfunction	1
Postoperative deaths	2
Total	57*(22.4%)

*Four patients had more than one complication.

evaluate our results to see if less radical methods of treatment produce acceptable results. As was shown earlier in this study, a significant number of patients treated with what today would be considered inadequate therapy, i.e., vulvectomy alone, did survive for a significant period of time without apparent recurrence of disease. The argument as to whether or not lymphadenectomy should be done has been widely debated,[1-6] with most authorities feeling that it is of definite value. What is still controversial, however, is the routine use of pelvic lymphadenectomy. Between the years 1955 and 1965, we routinely performed pelvic lymphadenectomy as an integral part of operation in all patients with vulvar carcinoma. As indicated earlier, only four of 51 patients had positive pelvic node disease. These findings have influenced us in abandoning the routine use of pelvic lymphadenectomy and reserving it for those cases in which positive inguinal-femoral nodes are found at the time of surgery or if the

lesion is clitoral in origin. We believe that, with the above exceptions, the infrequent occurrence of involved pelvic nodes in early stages of disease does not justify the potentially increased surgical morbidity.

What is needed is a better method of identifying those patients who require pelvic lymphadenectomy so that better individualization of treatment can be made. Clinical assessment of lymph node involvement preoperatively has shown error rates ranging from 13% to 39%.[2, 7]

It behooves us to constantly seek better and less traumatic methods for the treatment of this disorder. For these reasons, we are currently evaluating the use of radiotherapy to convert inoperable lesions to operable ones and also in lesions located in the area of the posterior fourchette which were previously treated with radical vulvectomy and an exenteration-type procedure. There is little doubt that radical vulvectomy and lymphadenectomy are disfiguring procedures and can produce serious sexual and marital dysfunction, particularly in the younger patients. For these reasons, we are also evaluating the possible role of megavoltage irradiation to enable us to be less radical with our surgery. Detailed analysis concerning the radiotherapy methods and results at our center is the subject of another report currently under preparation.

Finally, our experience indicates that a degree of individualization in the treatment of squamous carcinoma of the vulva can be achieved with acceptable results.

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Discussion

Dr. Wilson Footer, Oakland, California. Individualization of treatment is the key phrase in discussions of carcinoma of the vulva today. No one wants to come out and say that the classical routine treatment consisting of radical vulvectomy and en bloc dissection of the superficial and deep inguinal-femoral nodes and the pelvic nodes should be abandoned. For the woman with spread of vulvar malignancy to the inguinal and iliac nodes, and no further, it is the ideal treatment. But to subject every patient to that routine has indicated a nonanalytic approach.

I abandoned the shield incision in 1942 when I had such an incision break down. Since then I have performed the vulvectomy separately and then proceeded to the groin dissection on the side of the tumor and in many instances the opposite side because of central location of the primary or because positive nodes were found on the first side. When inguinal nodes were positive, if the patient's general condition permitted, deep inguinal and pelvic node dissections were performed. No patients, other than those with melanomas, have had recurrences in the tissue between the inguinal and vulvar incisions. In 1975, Ballon and Lamb recommended this use of separate vulvar and inguinal incisions and found no increase in tumor recurrence.

The authors stated that no patient with a lesion less than 2.5 cm in greatest diameter had nodal disease. I wish we could rely upon size alone, but we cannot. Figge found that 10% of lesions less than 2 cm had nodal involvement. Others have quoted various percentages of patients with lesions less than 1 cm who had positive nodes. I operated upon one patient with a lesion slightly more than 1 cm who had one positive node in the femoral canal. Size of the primary tumor can not be relied upon to decide to forego groin dissection.

Ideally treatment should be individualized. Wide excision of the lesion and a separate incision for the groin dissection on that side are the minimum that should be considered in the otherwise healthy patients. Then, if positive nodes are encountered, deep inguinal and pelvic lymphadenectomies are done and the step approach is carried out on the opposite side. That is, if the inguinal nodes are negative, the pelvic lymphadenectomy is not done; if positive, it is done.

It has been recommended that lesions involving the clitoris require pelvic lymphadenectomy even if the inguinal nodes are negative because of direct lymphatic spread bypassing the inguinal nodes. The experience of Way tends to negate this recommendation. In 1977, Piver and Xynos came to the same conclusion as Way and stated that the surgical treatment of carcinoma of the clitoris does not differ from that of other locations of carcinoma of the vulva.

Such modalities as radiation to the nodal areas, local applications of 5-fluorouracil, systemic chemotherapy, cryosurgery, and laser therapy should be thought of if only to be discarded as inappropriate for the individual patient. Finally there are some patients who are better off if no treatment is undertaken.

Reconstructive surgery has a definite place for certain women either as a modification of the repair of the original vulvectomy or as a secondary procedure.

Dr. Turko (Closing). I believe one key to the man-

agement of this disease is to consider a more flexible approach. Over the past 25 years we have been impressed that this may be appropriate in lesions involving the posterior fourchette and encroaching on the anal sphincter. Traditionally the rectum has been sacrificed in such instances but we now have seven cases treated by preoperative radiation to this area, followed by a radical vulvectomy and node dissection. In these cases the surgical specimen has revealed no residual disease in the perineal area. In January, I had the pleasure of appearing on a panel with Mr. Stanley Way and we discussed this concept. Mr. Way feels very strongly that surgery is the tnly method of treatment for vulvar carcinoma but he also indicated that in the future he might well consider preoperative irradiation in some instances. We have also recently begun to use postoperative megavoltage irradiation to the pelvis in cases that have proved to have unsuspected positive inguinal nodes and where a deep node dissection was not performed. Our early results are quite encouraging.

When one reviews the literature one sometimes encounters the statement that deep node dissections are associated with no increased morbidity or increased operative time. One can only wonder at the type of deep node dissection that is being carried out in such instances. The description in one paper suggests a digital dissection through the fossa ovalis. It has been our feeling that if a deep node dissection is performed it must involve a wide exposure extraperitoneally with a thorough dissection to the level of the common iliac bifurcation.

The value of intravenous urography prior to abdominal hysterectomy for gynecologic disease

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Negligence and failure to "test timely" are the two most common charges in obstetric and gynecologic malpractice suits. Both charges are often made in cases involving urinary tract injury during gynecologic surgery. These injuries occur most commonly during abdominal hysterectomy. This report is a 6 year study of 170 consecutive abdominal hysterectomies to ascertain the value of routine preoperative urography in preventing urinary tract injuries. As a control, 260 consecutive abdominal hysterectomies were performed without preoperative urography. There was one ureteral transection in the control group, but unrecognized urinary tract injuries did not occur in either the study or control group. The risks, costs, and benefits of urography are analyzed. (AM. J. OBSTET. GYNECOL. 134:208, 1979.)

A RECENT REVIEW of 1,852 malpractice suits against physicians noted negligence and failure to "test timely" as the two most common charges in these cases.[1] Injuries to the urinary tract during pelvic operations frequently result in a charge of negligence against the operating surgeon. In gynecology, these injuries occur most commonly during abdominal hysterectomy.[2]

A survey of local attorneys who are called upon to defend surgeons in negligence cases involving urinary tract injuries reveals they are often faced with the added charge of failure to "test timely." A plaintiff's attorney in these cases has little difficulty in locating expert witnesses willing to testify that a preoperative intravenous urogram might have prevented the injury.

That such testimony can be readily obtained is not surprising. The intimate embryologic and functional association of the genital and urologic systems is well recognized.[3] Intravenous urography is well established in gynecology as a prerequisite in the staging of invasive cervical carcinoma.[4] It is also a useful diagnostic procedure for the detection of recurrent carcinoma of the cervix.[5]

Two articles have appeared in the world medical literature recommending routine preoperative urography for all patients scheduled to undergo major gynecologic operations.[6, 7] Both of these articles cite the detection of unsuspected renal and extrarenal pathology as the reason for this recommendation.

The purpose of this 6 year study of 430 consecutive abdominal hysterectomies for gynecologic disease was to ascertain the value of preoperative urography in preventing urinary tract injury.

Material and methods

Making available or denying a potentially beneficial preoperative diagnostic test in order to conduct a prospective study presents both an ethical dilemma and a medicolegal hazard. In this study the ethical dilemma was solved by matching surgeons rather than patients.

The subject group of 170 patients were all operated upon by one surgeon during the 6 year period January 1, 1972, through December 31, 1977. All of these patients underwent intravenous urography on the day prior to scheduled abdominal hysterectomy. This routine screening procedure was an established part of the surgeon's preoperative workup and was not a deviation from his customary practice.

During the same 6 year period, the 260 patients in the control group were all operated upon by a second surgeon. None of these patients underwent preoperative intravenous urography. Again this was not a deviation from this surgeon's usual routine.

Both surgeons are Board certified and of the same age. They are products of the same medical college, internship, and residency training program. Both have practiced independently of each other in the same community for 20 years and admit all of their patients to the same hospital. Neither surgeon performs so-

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called prophylactic or elective hysterectomy. In other words, no operations in either series were performed for uterine cancer prophylaxis, contraception, or menstrual inconvenience.

Both ovaries were removed in more than 80% of the 430 patients. There was a final diagnosis of malignancy in 107 (25%) of the cases.

The average age in the subject group was 47.1 years; in the control group it was 46.9 years. The youngest patient in either series was 26; the oldest was 78. Both of these patients were in the control group and were operated upon for adenocarcinoma of the endometrium.

There were 1,893 abdominal hysterectomies in the hospital during the same 6 year period. The average age of all patients undergoing abdominal hysterectomy was 44.1 years.

Surgical technique. Both surgeons employ the same techniques with respect to verifying the location of the ureters. In all cases, the ureters are identified at the pelvic brim, and their location on the floor of the pelvis is determined by visualization and/or palpation.

In cases in which there is anatomic distortion due to the disease process, the ureters are dissected out before the hysterectomy is performed. In some cases with extensive pelvic floor disease, this dissection is not always feasible. In these cases, or in any case in which the possibility of ureteral or bladder injury exists, the following routine is carried out. At the completion of the operation, but before abdominal closure, the anesthesiologist intravenously injects 5 cc of indigo carmine. While this is being done, the circulating nurse distends the urinary bladder with normal saline instilled through the indwelling catheter. A cystotomy is performed in the distended urinary bladder. It can then be verified under direct vision that dye-stained urine is being ejected through both ureteral orifices. If the ureters are intact, the bladder and abdominal wall are closed. Intravenous indigo carmine and cystotomy produced no complication in any patient.

Results

No urinary tract injuries occurred in the study group of 170 patients in whom preoperative intravenous urography was done. The preoperative studies did demonstrate a 2.9% incidence of congenital anomalies. There were four instances of ureteral duplication and one renal agenesis. No other significant renal or extrarenal pathology was demonstrated. There were 17 (10%) minor reactions to the intravenous contrast agent, but no severe or fetal reactions occurred.

There was one ureteral transection in the control group. This injury occurred in a 73-year-old patient during the debulking of a Stage III serous cystadenocarcinoma of the ovary. The injury was recognized immediately and repaired; it healed without sequelae. This patient died of ovarian disease 3 years after operation and subsequent chemotherapy.

There was one case of carcinoma of the left kidney in the control group. This was in a 52-year-old patient being operated upon for atypical adenomatous hyperplasia of the endometrium. The asymptomatic carcinoma of the kidney was discovered during routine intra-abdominal exploration at the time of the hysterectomy. She is alive and well 2 years after irradiation and left radical nephrectomy.

There were only two intravenous urographic studies done in the control group of 260 patients, and these were done postoperatively on the two patients noted above.

Comment

Before any procedure becomes established as a routine in medical or surgical practice, the risk/benefit and cost/benefit ratios must be evaluated.

There are two risks associated with intravenous urography: reaction to the contrast agent and radiation exposure. Although no patient in this small series experienced a severe or fatal reaction to the intravenous injection of the contrast agent, tragic results have been reported. A review of 318,500 examinations using contrast media revealed a severe reaction in 1:14,000, and death in 1:40,000.[8] Of special interest to physicians caring for an aging population, this same study noted a marked increase in severe and fatal reactions in patients aged 50 or older.

The second risk concerns the long-term effects of the radiation received at the time of the x-ray study. This risk is impossible to evaluate, but it has been shown that four 14 by 17 inch x-ray views at 110 kV(p), 7.2 mamp 40 inch target skin distance produces 0.107 rads internally.[9]

The cost of routine preoperative intravenous urograms can be readily calculated. There were 1,893 abdominal hysterectomies in the hospital during the 6 years of this study. If the test has been routinely performed on each patient, at $100 per examination, the cost would have been $189,300. If the 1,893 patients had all been admitted to the hospital one day early, in order to perform the study, the cost would soar to over $400,000.

It is revealing to project these cost figures nationally for the same 6 year period as in the present study. Hysterectomy is the most frequent major operation performed in the United States, and as far back as 1973, 688,000 hysterectomies were performed.[10] This

number was also noted to be increasing, so a yearly average of 700,000 for the 6 years of this study would be conservative. This translates into 4,200,000 hysterectomies during the 6 year period January 1, 1972, through December 31, 1977. Using $100 as the cost for each examination, this results in a 6 year cost for this one diagnostic study of $420 million. If these patients had been admitted one day early and had postoperative intravenous urography also been done, the total 6 year cost would approximate $1,500,000,000.

There appear to be three benefits that might derive from preoperative intravenous urograms. These are defense against malpractice suits, the demonstration of unsuspected renal or extrarenal pathology, and prevention of urinary tract injury at the time of operation.

The first of these possible benefits is to the physician and not to the patient. In the medicolegal climate in which medicine operates today, it has become commonplace to order multiple tests that might be of value as a defense in malpractice suits.[1] Using preoperative and/or postoperative intravenous urograms solely as a defense against the charge of failure to "test timely" seems impossible to justify in the face of the risks and costs involved. Futhermore, it has been shown that physicians cannot find protection by ordering a battery of tests for the purpose of avoiding malpractice suits.[1]

That preoperative intravenous urograms can, and do, demonstrate previously unsuspected renal and extrarenal pathology is undeniable. It is also undeniable that careful abdominal exploration at the time of surgery has similar capabilities. Exploration has two distinct advantages: there is no cost and virtually no added risk.

It might be argued that the conventional intravenous urographic study has the capability of evaluating renal function, but this is not the case. Reports have shown that excretory urograms are not capable of quantitating the functional status of the kidney.[11] The ordinary intravenous urographic study simply depicts the structure of the urinary collecting system.

With respect to the test's benefit in preventing injury at the time of surgery, no urinary tract injuries occurred in the study group, while there was a ureteral injury in the control group.

At first glance, these results might seem to indicate a positive value for preoperative intravenous urograms. On closer analysis, this is not the case. In the control group where the ureteral transection occurred, the ureter was in its normal anatomic position. This injury was due to surgical error and not the lack of a preoperative x-ray examination.

This study, of an admittedly small group of patients, has failed to produce evidence that preoperative intravenous urograms are of value in preventing urinary tract injury at the time of abdominal hysterectomy.

The study does not conclude that preoperative intravenous urograms are never indicated in gynecologic surgery. It only questions their routine usage. This procedure, as well as a myriad of others, should only be prudently and selectively utilized.

A recent report states that most members of the medical profession are fiduciary failures.[12] Whether or not we physicians accept this, society is holding us increasingly responsible for both the physical and financial health of the patients we serve.

I wish to acknowledge the contributions of Thomas Murrieta, M.D. He made available the patients in the study group and also made valuable suggestions as to the final form of this report.

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Discussion

DR. CHARLES E. WEBER, La Jolla, California. Let us examine the two problems that Dr. Sack has defined in his straightforward, uncomplicated paper, void of graphs, tables, figures, and similar soporific material. The first is risk-to-benefit balance. It cannot be denied that a certain amount of risk is associated with the procedure. Dr. Sack has referred to the collective data of Ansell,[1] reflecting the incidence of reaction as 1 in 2,000 (mild), 1 in 14,000 (severe), and 1 in 40,000 (death). The deaths are seemingly age related, probably a function of myocardial susceptibility. Certainly, careful pretest screening for history of allergy or sensitivity together with selective pre-examination testing will eliminate the majority of reactions. Familiarity with reactions and prompt attention to treatment by the personnel involved with the testing can decrease the seriousness of the reactions which do occur. Dr. Sack presented no reactions in his series, and the data at Scripps Hospital in La Jolla are similar to those reported by Ansell,[1] although we have had no fatalities.

The benefits derived from intravenous pyelography can be broken down into two categories. The first is the detection of unsuspected urinary tract pathology, including congenital anomalies, pre-existing disease, and anatomic distortion associated with pelvic pathology; additionally, there is the detection of extrarenal pathology; additionally, there is the detection of extrarenal pathology. Dr. Sack referred to the data of Roden and colleagues, reflecting 22% unsuspected significant renal anomalies and 6.4% noteworthy extrarenal abnormalities. This represents six times the yield produced with routine chest film survey (4.6%).

I will, with your permission, resort to anecdotal data at this time. Mrs. M was admitted to Scripps Hospital for pelvic surgery because of uterine prolapse and pelvic floor relaxation; additionally, she had a large incarcerated umbilical hernia. Rather than the proposed surgery, the patient had resection of a parathyroid adenoma. The routine preoperative urogram revealed left renal and ureteral lithiasis. In the course of evaluation for this problem, serum calcium levels were obtained and reported as 11.1 (normal 8.4 to 10.6). The diagnosis of parathyroid adenoma then became quite simple and was proved in surgical specimen. Currently, she has been relieved of not only the parathyroid tumor but also the stones and, more recently, the prolapsed uterus and incarcerated unbilical hernia for which she originally sought help.

A 40-year old patient was admitted for hysterectomy because of uncontrollable menometrorrhagia and adenomyosis. The routine preoperative urogram demonstrated an unsuspected, nonfunctioning right kidney. After urologic evaluation, the proposed surgery was successfully carried out much to the relief of the physician and the satisfaction of the patient and her attorney husband.

And a patient was scheduled for anticipated pelvic surgery because of a right adnexal mass associated with an intrauterine contraceptive device and felt to be a unilateral pelvic abscess. Routine pyelography was done prior to the surgery, and Grade III hydroureter and hydronephrosis secondary to blockage of the ureter at the ureteropelvic junction from the pelvic mass were detected. The patient had the surgery. The urinary abnormality is slowly returning to normal.

I leave the implications of postoperative pyelography in these patients without prior knowledge of their preexisting urinary system abnormalities to your imagination and speculation. While these cases are certainly not commonplace occurrences and do represent anecdotal data, they are factual.

The second aspect of value of this procedure alludes to the operative benefits or prevention of urinary tract injuries during surgery because of the knowledge gained by intravenous pyelography. I agree wholeheartedly with Dr. Sack in his assertion that skillful surgical management of the procedure is the most important element in preventing any urologic complications. Pelvic, including urologic, anatomy must be thoroughly defined at surgery and careful attention must be paid to any suspected urologic injury. In this regard, the technique of operative intravenous urography has been refined by my associate, Charles F. Wright, M.D.,* and the radiology staff at Scripps Memorial Hospital in La Jolla. This has given us a simple, effective method for detecting suspected urinary tract injuries during surgery. Time does not allow my detailing the procedure, but it is well worth your attention.

Finally, is routine intravenous pyelography cost effective? To the individual patient with positive or negative findings and/or benefit from the procedure, the answer is a simple "yes or no." Obviously, the $400,000 to which Dr. Sack alludes could have been spent more effectively in other ways, so the overall answer is more evasive. But compare, if you will, the cost effectiveness of a simple test in daily use, a total of 4 million tests a year at a cost of approximately $80 million a year to detect 450 patients with positive and treatable disease at a cost of approximately $160,000 a case.[3] I refer, of course, to routine, mandated premarital serology. I am forced to provide the latter by mandate, but I shall continue to provide the former by choice.

*Unpublished data.

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DR. THEODORE W. LORING, Eureka, California. Initially, when I read the summary of Dr. Sack's paper, I felt he was going to end up recommending that we routinely use intravenous pyelography. However, I was very happy in reading the full manuscript to find out that he does not so recommend. Although he did have one transected ureter in the group, he pointed out that the intravenous pyelogram did not prevent this and would not have prevented it. I would like to take this opportunity to give you a bit of privileged information with regard to urinary tract injuries. I think that urinary tract injuries occur much more often then we realize. I serve as a director of Norcal Mutual Insurance Company and also have the privilege of being the obstetrics-gynecology reviewer of all claims that come into our office. Norcal Mutual represents approximately 5,200 physicians in northern California, excluding the Bay Area. Between the date of the formation of our company on November 1, 1975, to August 23, 1978, we had 1,248 claims or incidences, including suits, reported to the company. The claims involving our specialty amount to 228 cases of 19.1% of the total. Of these 228, 89 involve obstetrics, which is 39% of the obstetrics-gynecology claims or 7.5% of all claims the company has received. In gynecology we have had 139 claims—this is 61% of the claims involving obstetrics-gynecology or 11.2% of the total claims of the company. The gynecology group is somewhat alarming in that there were 23 cases involving urinary tract injuries, which is about 16.5% of all our obstetrics-gynecology claims. There is another factor that we must look at in time. We have 29 cases involving laparoscopic tubal sterilizations, 16.5% of all our gynecology claims. I would be the first to agree that these figures are relatively "green." Just what this will cost the company in time, no one can say. Many of them probably will not end up as suits. But at least some costs will be generated to the company. I hope in the future, as our material ages, that I will be able to present to you a more detailed report of where our specialty in with regard to malpractice. I am sure that all of the doctor-owned companies in California, in general, probably will have somewhat the same experience that the Norcal Mutual Company has had. For years I have felt, and I have argued the point, that gynecologists and obstetricians are unfairly rated by being put in a class always above general surgeons. I no longer feel that way.

DR, ROGER W. HOAG, Berkeley, California. The discussion of this paper reminds me of a case which happened in southern Alameda County, in which a woman's abdomen was being explored for a pelvic mass. The surgeon proudly removed this retroperitoneal mass and sent it up to the pathologist, who proceeded to slice it up before he sent back down a report—this was a horseshoe kidney. The surgeon had successfully removed the woman's only kidney. His operative note indicated he had felt her kidneys on manual exploration. She was transferred to Stanford Medical Center for dialysis in the hope of a renal transplant. But none was forthcoming and she died. Needless to say, the case was settled quickly. It seems to me that pyelography might have prevented this accident. I do not speak for routine pyelography. I would be opposed to it. But I think that any gynecologist embarking on a pelvic exploration or anything that might even remotely be a retroperitoneal mass should consider a pelvic kidney or horseshoe kidney and consider the advisability of preoperative urography.

DR. BRUCE B. ROLF, Los Angeles, California. Intravenous pyelography is not an innocuous procedure. The question is whether the added cost of this does warrant its routine use prior to simple hysterectomy. In my own practice, I have experienced one fatality and one near fatality due to anaphylaxis in diagnostic intravenous pyelography. I do believe that there is a place for preoperative intravenous pyelography prior to surgery for adnexal masses. In some instances ureteral catheters should be placed if difficult dissection due to previous pelvic inflammatory disease or postoperative adhesions is anticipated. The urologists in our community in the event of ureteral ligation lament that a pyelogram was not obtained previously. In performing pyelography, it is appropriate that a physician be present either to inject the dye or to take care of possible anaphylactic reaction.

DR. RALPH H. WALKER, North Hollywood, California. Several years ago, when Dr. Dick Simmons was in Los Angeles, he made the remark that most of the cases referred to the Mayo Clinic for ureteral repair after damage were of ureters that were not in the normal location, which had been cut for that reason. In our own care, if there is any adnexal disease that seems to involve the ureter, we utilize ureteral catheters prior to surgery. In those patients who have been operated upon previously and have a large enterocele or vaginal prolapse requiring vaginal plastic repair, we routinely place ureteral catheters prior to surgery and it is amazing in our findings that many of those ureters are not in average or "normal" anatomic locations.

DR. SACK (Closing). What I am going to say may not be fair, but it is also apropos of what we talked about—the malpractice situation and the situations we are encountering, but I am almost afraid that we have changed the old axiom from "physician heal thyself" to "physician treat thyself."

Office termination of pregnancy by "menstrual aspiration"

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A program of office menstrual aspiration was initiated in our institution in 1972. Since that time 1,443 patients have been admitted into the study. These patients were evaluated by age, marital status, gravidity, repeat pregnancy terminations, complications, and detailed tissue analysis as well as contraception utilized at the time of conception and following counseling after the procedure. A majority of these patients were less than 25 years old and single; 28% had had a previous termination and 51% a previous pregnancy. Pathologic evaluations revealed Arias-Stella reaction in 78%. When these data were compared to those of a similar group of women whose pregnancies were terminated in the hospital by suction curettage, it was found that the office procedure is comparatively safe and should therefore be the therapy of choice. (AM. J. OBSTET. GYNECOL. 134:213, 1979.)

IN AUGUST, 1972, a pilot project for the office termination of pregnancy was initiated in the outpatient department of Kapiolani Hospital. The initial findings for the first 181 cases were presented in 1973[5, 8] and led to the conclusion that this procedure was a safe, effective, low-cost method for the termination of early pregnancy. As a result, the study was enlarged and the office procedure compared to the standard hospital suction curettage. An additional 1,262 patients have been admitted to the study since that time for a total of 1,443 patients who have been evaluated.

Material and methods

All of the patients in this study were sexually active and were self-or-physician referred because of delayed menses with or without a positive pregnancy test. Each patient was seen initially by our nurse-practitioner and asked to complete a health questionnaire. The patient then received a detailed explanation of the procedure utilizing audiotapes, pictures, and verbal clarifications. All questions were answered and the patient was then asked to sign an informed consent.

Next a pelvic examination was performed and uterine size was determined. Patients who were estimated to be 8 weeks gestation or less from the day of the last normal menstrual period were admitted to this study and had a blood type and Rh determination. Those who were estimated to be 9 weeks or beyond were scheduled for a hospital suction curettage with general anesthesia.

The menstrual aspiration procedure was preceded by gentle cleansing of the vagina with a povidone-iodine* solution. This was followed by a paracervical block utilizing a total of 16 cc of 1% lidocaine, 4 cc at 3, 5, 7, and 9 o'clock. After satisfactory anesthesia was obtained (at approximately 5 minutes), the anterior lip of the cervix was grasped with an atraumatic tenaculum. With a "no-touch"[7] technique, a 5 mm sterile catheter was then inserted and suction induced with a 50 cc Karmann-type syringe. In some instances, a 6 mm catheter and, on a few occasions, a 7 mm catheter were utilized. All tissue and fluids removed were

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*Betadine, Purdue Frederick Co., Yonkers, New York.

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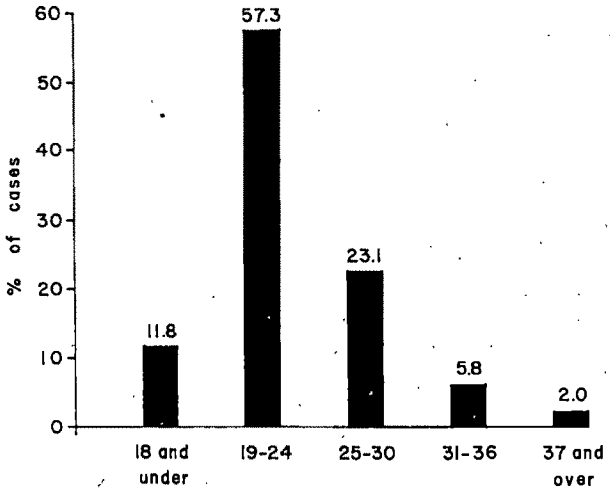


Fig. 1. Age of patients at time of procedure.

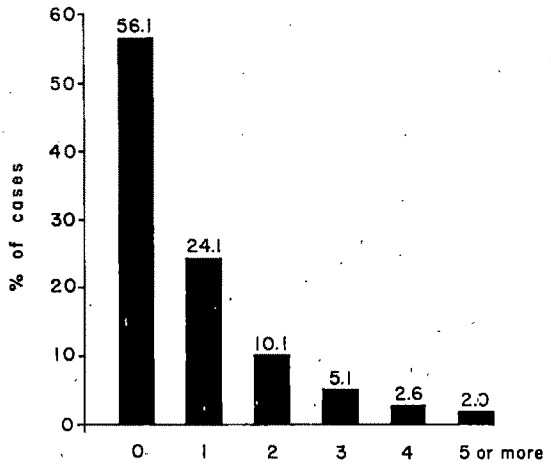


Fig. 2. Previous pregnancies.

carefully measured and sent to our pathologist for evaluation. The patient remained at rest in the examination room for at least 30 minutes following completion of the procedure before she was allowed to leave. All patients were instructed in daily temperature recordings. If the patient was Rh negative, she was routinely given an injection of Rhogam.* The patient was specifically instructed to return or call immediately if any complication arose. A routine follow-up visit was made and a pregnancy test was performed 2 weeks after the procedure.

In an attempt to compare the results obtained by the office procedure with those of in-hospital abortions, we instituted a prospective study of 400 in-hospital abortions which were 8 weeks' gestation or less, and additionally we reviewed the statistics obtained for all hospital abortions in Hawaii over a 4 year period by the Hawaii Pregnancy, Birth Control and Abortion Study. We were unable to obtain the same detailed information for these two studies that we did for the office procedure since most patients had only a brief history related to the procedure.

Results

A total of 1,443 patients had a termination of pregnancy by office suction curettage between August 30, 1972, and May 1, 1977.

In our series, 69% of the patients were less than 25 years of age while 7.7% were 31 or older (Fig. 1). When marital status was considered, 73.5% were single, 16% married, and the remainder widowed, divorced, or separated. A majority (56%) of our patients had no previous pregnancies (Fig. 2) while 25 had five or more. In addition, 22% had a previous abortion and 11% a previous menstrual aspiration.

An assessment of the contraceptive method utilized at the time of conception was made as well as the method preferred following counseling and at the 14 day follow-up visit (Fig. 3). At the time of conception, 44.5% reported they were not utilizing any form of contraception, 4.8% were using an oral contraceptive, 2.5% an intrauterine contraceptive device, 7% a diaphragm, and 17% condoms; two patients reported a failure using the Encare Oval,* and the remainder had used a combination of foam, jelly, withdrawal, and rhythm. Following the procedure and our counseling session, 52% of the patients elected to use oral contraceptives, 14% the IUD, and 10% a diaphragm. The remainder chose some other method. It was interesting that 9.7% chose no contraception and 2% chose abstinence, while 1.5% selected a sterilization procedure.

At the 2 week visit, 49.4% were using or planned to use oral contraceptives, 11.6% the IUD, 9.9% the diaphragm, 10.3% the condom, and the remainder some other form or no contraception. There was an 86% compliance to the 2 week follow-up office visit.

During the procedure, a measurement of the amount of aspirated contents was obtained. In 2% of the cases, aspirated material had a volume of over 100 cc. The maximum volume obtained was 535 cc of blood in one patient. This was retrospectively determined to be at 10 weeks' gestation. A total of 9.5% had 50 to 100 cc of fluid while the remainder had less than 50 cc, 20% having volumes between 30 and 50 cc and 68% having less than 30 cc.

Thirty-two patients (2.2%) had a repeat menstrual

*Rhogam, Ortho Pharm. Corp., Raritan, New Jersey.

*Encare Oval, Eaton-Merz Laboratories, Inc., Norwich, New York.

aspiration for initial failure to abort the pregnancy; two patients (0.1%) had two repeat procedures.

Immediate side effects occurred in only 6% of the patients. The major complaints were nausea and/or vomiting (2.1%) and vertigo and/or syncope (1.6%). Two patients (0.1%) had severe hemorrhage, one requiring an emergency suction curettage. Seven patients (4.8%) reported severe pain. There was one lidocaine reaction (0.06%) and one patient (0.06%) had a stenotic cervix that prevented insertion of the catheter. Additional problems occurred during the 14 day interval prior to re-examination in 13% of the patients. The most frequent complaints were prolonged or heavy bleeding (5%), prolonged or severe cramps (4%), and vaginal discharge (1.5%). Four patients (0.2%) reported an elevated temperature and eight (0.5%) reported chills. All of these patients were examined by a physician. Nine patients (0.6%) were determined to have incomplete abortions, with subsequent completion by repeat menstrual aspiration, intramuscular prostaglandin, or suction curettage. Three patients (0.2%) were found to have ectopic pregnancies; 15 patients (1%) were diagnosed as having endometritis. The remaining 27 patients (1.8%) were diagnosed as having some other condition, most of which were unrelated to the termination procedure or were of a minor nature requiring no therapy.

All tissue obtained during the procedure was sent for pathologic examination and results were compared with the pregnancy test. An Arias-Stella phenomenon was found in 78% of the tissue samples submitted. Of the remainder, 18% were determined to have been pregnant by other pathologic criteria and 4% were not pregnant. A positive pregnancy test occurred with a negative Arias-Stella phenomenon in only 56 (4.4%) patients.

Our study of 420 in-hospital terminations of pregnancy by suction curettage revealed 19% of patients to be over the age of 30 while 49% were less than 25 years old. In this group, 25% had no prior pregnancies and 44% had a prior abortion.

Side effects were encountered in 19% of the hospitalized patients. The most common problem was nausea and/or vomiting which occurred in 14% of the patients. Included in the remaining 5%, however, were two uterine perforations, a laryngospasm, and a cervical laceration. One of the uterine perforations required a hysterectomy. Three patients (0.7%) had subsequent curettage for heavy vaginal bleeding. No information was obtained on contraceptive usage before or after the procedure in this group.

Data obtained from the Hawaii Pregnancy, Birth Control and Abortion study[5] revealed that 22% of

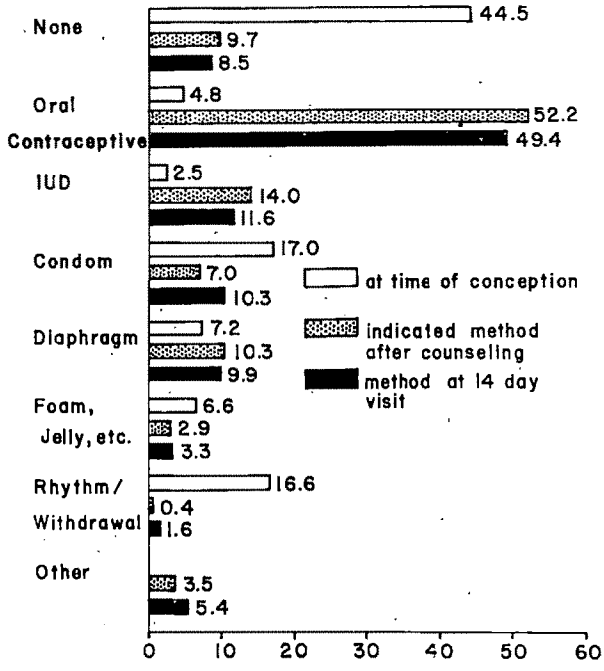


Fig. 3. Contraceptive methods used.

women seeking abortion were less than 20 years old, 34% were between 20 and 24 years old, 21% were between 25 and 29 years old, and 11% were over 30 years of age. It was found that 50.8% had had no previous pregnancies, 27% had two or less, and 22% had more than three. When marital status was considered, 61% had never married. There was a 6.9% complication rate, 75% of which were considered minor. Thirty-four percent of all terminations in this state were at 8 weeks' gestation or less and 31% were at 9 to 10 weeks.

Comment

Early termination of pregnancy is a simple procedure but is not withoout complications. Immediate side effects were experienced by 6% of our patients and by the 2 week visit 13% of the patients had experienced a complication. This rate is higher than that reported in some series[1, 3, 6, 10] but may be due to our detailed reporting and our concern with all effects, whether major or minor.

Of the 32 patients who apparently failed to abort, all had a subsequent procedure and two had the procedure repeated twice. Our failure rate was less than that reported in other series.[2] We believe this low rate was due to careful selection of patients and proficiency and experience gained through repeated procedures. There have been no failures in our last 400 cases.

We compared our percentage rate of side effects with that of the in-hospital abortions and found this prospective study revealed in-hospital abortions to

have a 19% incidence of side effects. The Hawaii[4, 9] study showed a 6.9% incidence of side effects. In both instances, the primary problem appeared to be nausea and/or vomiting which is also seen with the office procedure.

One potential serious complication encountered with the office procedure is excessive hemorrhage. In assessing uterine size, it is possible to misinterpret the history and examination, thereby attempting menstrual aspiration on advanced pregnancies. The one patient in our study who had a severe hemorrhage (over 500 cc) had a more advanced gestation than anticipated. After this incident, we had larger catheters immediately available, as well as oxytocin and intravenous fluids.

Our management of the other common complication, syncope and/or vertigo, has been the use of oxygen. We now keep an oxygen tank available in the office for immediate use.

As noted, the contraceptive practices of our patients were carefully recorded. A number of patients who had repeat menstrual aspirations had been seen by us previously and had been carefully counseled and given a method of contraception. Some of these patients specifically did not use the method for a personal or other reason and again became pregnant. It was also noted that the method selected at the time of the procedure, when motivation is theoretically highest, is frequently not the method that is used or desired 2 weeks later. Our investigations of all cases of repeat menstrual aspiration revealed a method failure in less than 10% of these patients. When contraceptive failures did occur, they were found to be associated with a change in contraceptive method or failure to use any method. It was particularly distressing to observe these repeated undesired pregnancies, since a large proportion of our patients were referred to us from a University student population. We are convinced that adequate counseling and availability of contraceptive methods by themselves will not completely prevent "unwanted" pregnancies.

Detailed histopathologic evaluation was performed on all tissue removed. We initially attempted to correlate the amount of tissue, length of pregnancy, and level of β-subunit of human chorionic gonadotropin but could not find any correlation.[7] In 78% of the patients, an Arias-Stella reaction was reported. This was assumed to be evidence of early pregnancy and after the first 200 cases we began to expect to see this histologic pattern. In those patients who were pregnant but did not have an Arias-Stella reaction, there was marked glandular hyperplasia as has been previously reported.[1] When a positive pregnancy test was obtained and included in the criteria for pregnancy, only 4% of the patients did not show the phenomenon. Two of the three patients with an ectopic pregnancy had the Arias-Stella phenomenon.

A problem which we encountered early in our study and is still unresolved is the appropriate name for this procedure. It has been called "menstrual aspiration," "menstrual regulation,"[3] "menstrual induction,"[8] and "menstrual extraction,"[1] as well as other names.[2] A common acceptable nomenclature such as "uterine aspiration" would assist in popularizing the procedure as well as in collecting complete statistics.

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Discussion

Dr. Roger R. Miesfeld, San Diego, California. I also had a problem with the nomenclature a number of years ago until I limited my definition to that proposed by the National Medical Committee of Planned Parenthood in its *Manual of Medical Standards and Guidelines.*[1] They use the term "endometrial aspiration," defined as follows: "Endometrial aspiration for the purpose of early termination of pregnancy is vacuum curettage of the uterus performed within 5 to 14 days after the expected date of menstruation in women in whom it is possible that unplanned, unwanted conception has occurred." This eliminates the term "menstrual" which suggests that menstruation is merely being induced. Menstrual dates are frequently unreliable and therefore I always do a pregnancy test. If

negative, I call it "endometrial aspiration"; if positive, I call it an "abortion." A positive test alerts me that more than 14 days may have passed after menstruation was expected and reminds me of the possibility of ectopic pregnancy, should the aspiration yield very little tissue. Actually I rarely use the term "endometrial aspiration" because we now have available in our laboratory a radioreceptor assay test for human chorionic gonadotropin which we use for patients 1 to 14 days after expected menstruation. This has practically eliminated doing a procedure which has been shown to be unnecessary in as many as 50% of patients since they were in reality not pregnant. Another point that might be made is that the Joint Program for the Study of Abortion,[2] under the auspices of the Center for Disease Control, shows a higher total complication rate for abortions performed at 6 weeks or less than when done at 7 to 8 weeks. Therefore, it might be prudent to wait for a positive urinary chorionic gonadotropin test to lower the complication rate, decrease the number of unnecessary procedures, and decrease the number of failed abortions.

In both the hospital and office groups, the authors' total complication rate is rather high when compared to that in the Center for Disease Control report.[2] However, it appears that these were mainly quite minor complications and I doubt that most of us would have conscientiously reported many of the minimal and minor side effects. It was encouraging to note no major complications in the office group, unless the lidocaine reaction was severe, the patient with 500 cc of blood loss required a transfusion, or the four patients with an elevated temperature showed evidence of a serious infection. In the hospitalized patients, one would expect a high incidence of nausea and vomiting because of the use of general anesthesia. The serious complications of uterine perforation and cervical laceration are also more likely to occur with general anesthesia than with paracervical block. The one major complication, the uterine perforation requiring hysterectomy, is compatible with the major complication rate reported by the Center for Disease Control. I can only surmise that the high total complication rate reflects very conscientious reporting and the low major complication rate indicates a high degree of skill of the operators.

The availability of oxygen and oxytocin was mentioned. I assume the rooms also have an adequate supply of drugs, intravenous solutions, and resuscitative equipment. Preoperative sedation is usually not necessary for the early terminations. However, since I have been using diazepam, 5 to 10 mg intravenously, I have seen a marked decrease in discomfort, and, as has been reported, it helps protect against toxicity by raising the anesthetic seizure threshold. After reading the report of Grimes and associates on five deaths due to paracervical anesthesia used for first-trimester abortion, we now have an emergency "crash cart" in the room whenever we perform an abortion. One point that was not clear to me pertains to the criteria for establishing a diagnosis of pregnancy. The authors reported that 4% were not pregnant. This seems very low when including the 5 and 6 week gestations, unless there were very few in this early group. Also they stated that "in 78% of the patients, an Arias-Stella reaction was reported. This was assumed to be evidence of early pregnancy." Novak[4] stated in *Clinical Obstetrics and Gynecology* that "ASR has been noted after administration of contraceptive pills and clomiphene and occasionally as a physiologic response to the hormones elaborated during a normal cycle. While highly suggestive, it is not pathognomonic of pregnancy." Would Dr. Hale please clarify this point for us?

Since 14% of the patients were lost to follow-up, is it possible that a significant number of complications could have occurred in this group and thus changed the complication rate? Now that you have gained so much experience with early termination, do you plan to do abortions up to 12 weeks as an office procedure?

Finally, although a major medical breakthrough has not been presented, it was reassuring to hear that office abortion carries minimal risk and perhaps has less major complications than do hospital abortions.

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DR. HAROLD M. LYONS, Merced, California. There is only one thing that I think we should bear in mind, and that is the problem concerning the Arias-Stella reaction. It is perfectly all right to be partisan about it and to feel strongly that it is useful, or not useful, but do not let anybody write it down, because at the present time medical-legal authorities and malpractice lawyers are having a field day with it. If it appears in a report, it is a presumption of pregnancy which cannot necessarily be proved. If operation is performed for an ectopic pregnancy on the basis of an Arias-Stella phenomenon, and there is no ectopic pregnancy, a suit is likely. We should vocalize this whenever we want, but I think we should keep it out of the written record.

DR. HALE (Closing). Dr. Miesfeld has had a great deal of experience in this area and I was interested to hear what what he said. I will mention one of the problems to be faced in a patient who comes in for "endometrial aspiration." As the length of amenorrhea increases the accuracy of the pregnancy test increases and yet the probability that a patient is pregnant is still only about

94 to 95% even with a positive test. If you look at that another way, the duration of amenorrhea in days, the chance of pregnancy increases almost proportionally to the length of time the patient is amenorrheic. I think that is interesting information to us, because that is why we have determined we would not use the Planned Parenthood definition of endometrial aspiration. We wait now for a positive pregnancy test or until we are absolutely certain in our own minds that pregnancy has taken place. We also do not use the term "endometrial aspiration" because insurance carriers get that confused with endometrial biopsy. I do agree with you that hopefully we can come up with a standard definition. I believe our complication rate is higher because we were looking for complications. We specifically asked patients questions such as: "Did you hurt?" "Did you have bleeding?" "Did you have this or that?" because we wanted to overload our statistics in the realm of what might have been the ultimate, or the maximum number, as opposed to just what patients reported to us. To answer the other questions, the lidocaine reaction was very minor. No patient required transfusion. I was very interested in the comment about preoperative diazepam and think perhaps that might be something we should consider because these patients are highly apprehensive. We do use diazepam in our patients who are going in for hospital abortions and we find that it does reduce anxiety. In terms of the question asked about the diagnosis of pregnancy and the Arias-Stella phenomenon, I want to point out that we had this in 78% of patients; in those who did not have this we used another way in which we could assess pregnancy. This was by either an extreme hypersecretory pattern or test of the beta subunit of human chorionic gonadotropin. Since this last test is not something I would recommend every individual in private practice order, because of the cost, we are comfortable just in looking for abnormal findings. Dr. Lyons, we are only describing it here for your information. There were few patients in whom pregnanccy could not be determined by the use of histopathologic criteria. We did have 14% lost to follow-up. We made every effort to observe these patients and many who were lost to follow-up were not really lost. The patient just did not come back. We got in touch with the attending physician or we got in touch with a roommate or boyfriend, etc., but not the patient. I do not believe that you can use this kind of follow-up in a statistical analysis because you really did not see the patients and you really did not talk to them. In answer to the question about 12 weeks' gestation, I will simply say that I would not be worried about a patient who lost 500 cc of blood. We do very carefully select these patients and we now also have a suction machine in the office just in case we get into trouble and need it. However, I do believe that one has to be highly selective in terms of any pregnancy beyond 6 weeks that will be terminated in the office.

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Pretreatment lymphangiography and operative evaluation in carcinoma of the cervix

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Ninety-five patients with cervical carcinoma who were not candidates for definitive operation underwent initial lymphatic and 24-hour nodal phase lymphangiography and lymphadenectomy prior to radiation therapy. Operation by a transperitoneal or extraperitoneal approach consisted of bilateral pelvic and periaortic lymphadenectomy, exploratory laparotomy, and intraperitoneal biopsies as indicated by the findings. Radiation therapy was modified to include proved sites of metastases. Intestinal injuries followed transperitoneal operation and radiation therapy but were uncommon in patients in whom exploration was done by the extraperitoneal route. Eighteen patients (19%) had unsuspected metastases to common iliac or periaortic lymph nodes identified at operation. The characteristics of the primary tumor and the interpretation of the lymphangiogram provided an inaccurate basis on which to modify treatment. As further studies confirm the risk of disseminated disease in those patients with metastases to common iliac and periaortic lymph nodes, future treatment plans might incorporate adjuvant chemotherapy or immunotherapy in addition to extended-field irradiation. (AM. J. OBSTET. GYNECOL. 134:219, 1979.)

CARCINOMA OF THE CERVIX, if untreated, spreads to involve adjacent tissues and lymphatic metastases to pelvic and periaortic nodes are common. Occasionally, metastases by the hematogenous pathway involve lung, bone, and other distant sites. The currently accepted staging of carcinoma of the cervix is based on a clinical and limited radiographic assessment of the extent of the primary tumor.[1] Spread to adjacent organs is identified by pelvic examination, cystoscopy, intravenous pyelography, sigmoidoscopy, and barium enema. Chest roentgenogram, skeletal survey, and tests of hepatic function aid in the detection of distant metastases. No provision exists to determine the volume of the primary tumor independent of stage and the presence of metastases to the pelvic and periaortic lymph nodes.

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This report compares the results obtained by lymphangiography and lymphadenectomy in the pretreatment evaluation of the regional lymph nodes and subsequent modification of therapy in patients with carcinoma of the cervix.

Material and methods

One hundred three patients with carcinoma of the cervix underwent pretreatment operative evaluation which consisted of abdominal exploration and pelvic and periaortic lymphadenectomy. Bipedal lymphangiography was performed in 95 of the 103 patients who comprise the study group. Four of the eight patients excluded from this report refused lymphangiography, in two the lymphatics could not be cannulated, and in two the radiographic study was unsatisfactory.

After identification of the individual lymphatic vessels by the intradermal injection of patent blue violet dye into the first web space, an incision over the dorsum of the foot facilitated their isolation and cannulation. Six millimeters of Ethiodol was infused slowly and initial flow pattern studies and delayed films of opacified lymph nodes were obtained. A filling defect in a node not traversed by lymphatics constituted definite

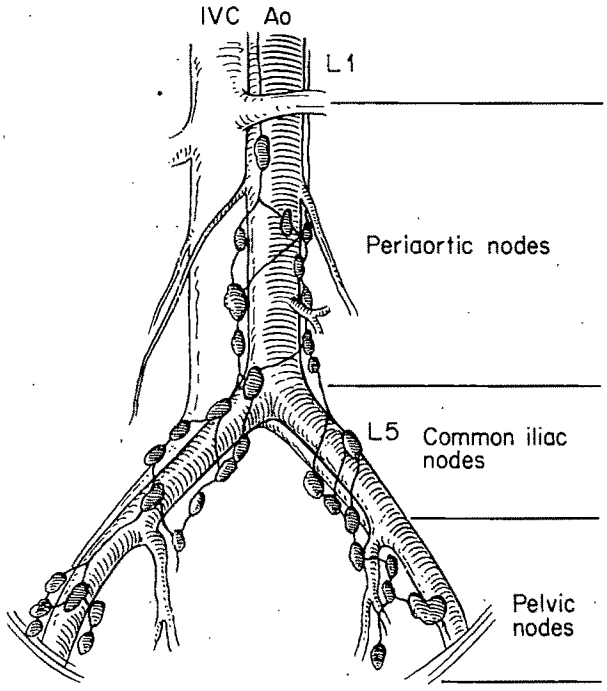


Fig. 1. Pelvic nodes include hypogastric, external iliac, obturator, and gluteal nodes. Common iliac and periaortic nodes are grouped together for analysis.

lymphangiographic evidence of a metastasis. Complete replacement of a lymph node and lymphatic obstruction with or without collateral circulation were viewed as indirect evidence of metastatic spread. In the absence of these findings, the lymphangiogram was classified as negative.

Operative evaluation included a careful exploratory laparotomy with combined abdominal and transvaginal palpation of the primary tumor, intraperitoneal cytologic washings, and indicated biopsies. Early in the series, exploration was performed through a vertical, midline hypogastric incision with node biopsies obtained through incisions in the posterior parietal peritoneum. Unacceptable morbidity when this was combined with radiation therapy resulted in the design of an extraperitoneal approach to these node-bearing tissues. This technique, previously described, utilizes a left-sided J-shaped incision and medial reflection of the peritoneum from the underlying vessels.[2] Lymph nodes obtained from bilateral obturator, hypogastric, external iliac, and common iliac and periaortic regions are submitted for separate pathologic evaluation. The presacral space, easily visualized by the extraperitoneal approach, also is dissected. Postoperative abdominal roentgenograms confirmed the adequacy of resection in each of the node-bearing areas.

Table I. Lymph node metastases in patients with cervical carcinoma

	Pelvic nodes		*Common iliac and aortic nodes*		*Total patients (No.)*
Clinical stage	*No.*	*%*	*No.*	*%*	
IB	6	27	5	23	22
IIA	6	38	3	19	16
IIB	5	16	6	19	32
IIIA	1	100	0		1
IIIB	8	35	4	17	23
IV	0		0		1
Total	26	27	18	19	95

Table II. Comparison of lymphangiogram and lymph node biopsies

	Lymphangiogram		
Lymph-adenectomy	*P neg./ C-A neg.*	*P pos./ C-A neg.*	*P neg. or pos./C-A pos.*
P neg./C-A neg.	52*	10	5
P pos./C-A neg.	5	3*	2
P pos./C-A pos.	5	3	
P neg./C-A pos.	1	0	9*

*Agreement.

Results

The operative approach was transperitoneal in 30 patients and extraperitoneal in 65. Small intestinal injuries occurred from 2 to 17 months following operation and radiation in nine of 30 patients (30%) undergoing exploration by the transperitoneal approach. All required further operative intervention and three died of complications. Small intestinal injury requiring resection was noted in one patient in whom the extraperitoneal approach was utilized. Complications of small bowel function were unrelated to the radiation field employed as only one of these 10 patients received radiation therapy to the periaortic region. No significant difference in blood loss, hospital stay, or interval from operation to initiation of radiation therapy existed. Morbidity from lymphangiography was confined to transient discomfort and sterile inflammation at the site of the incision. Pulmonary insufficiency was not observed.

Operative findings detected disease more advanced than the clinical stage in 32 patients (33.6%). In two patients, disease was less than determined by the clinical stage. Of the 32 patients with more extensive tumor,

one had metastases to the ovary and one, to the omentum. Two had extension to the pelvic side wall not detected on bimanual examination and the remaining 28 had unsuspected metastases to pelvic and/or periaortic lymph nodes. Both patients with less advanced disease had pelvic endometriosis as the basis of the discrepancy.

Because metastases to common iliac and periaortic lymph nodes were used as a basis for modification of radiation therapy, these areas were considered together in evaluating results (Table I). Pelvic lymph node metastases were present in 26 patients (27%), with common iliac and periaortic nodes involved in 18 patients (19%). Only two patients with metastases to the common iliac or periaortic lymph nodes had no metastases to the pelvic nodes.

Radiation therapy was modified on the basis of operative findings in 23 patients (24%). Seventeen of 18 patients with metastases to the common iliac or periaortic lymph nodes had 4,320 to 5,120 rads delivered to the level of the twelfth thoracic vertebral body, as previously described.[3] Six patients with pelvic lymph node metastases had an increase in the external component of radiation therapy.

For purposes of analysis, a lymphangiogram was designated as P negative or positive based on the status of the pelvic lymph nodes and C-A negative or positive following evaluation of the common iliac and periaortic nodes (Fig. 1). Results of the lymphangiogram were then compared with the lymphadenectomy specimens from these areas (Table II). Fifty-two patients in whom the lymphangiogram was P negative/C-A negative had no metastases demonstrated at lymphadenectomy. In five patients pelvic lymph node metastases were identified; five patients had metastases to both pelvic and periaortic nodes, and one patient had a metastasis to a periaortic lymph node. Sixteen patients had a lymphangiogram designated as P positive/C-A negative. Biopsies were in agreement in three patients but revealed no metastases in 10 and disease in both pelvic and periaortic lymph nodes in three patients. Sixteen patients had a lymphangiogram interpreted as P negative or positive/C-A positive and in nine of these lymph node biopsies confirmed disease in this area. In seven patients, however, no periaortic lymph node metastases were demonstrated and five of the seven had negative pelvic lymph nodes as well.

In 64 patients (67%) agreement existed between the two diagnostic approaches. Fifteen patients (16%) had disagreement in the form of a false positive or negative lymphangiogram in the pelvis alone. False negative and false positive results were approximately equal in their distribution among the various clinical stages, with false negative results somewhat more common in the early stages and false positive results more common in women with advanced disease.

Comment

Metastases to the common iliac and periaortic lymph nodes occur frequently in patients with advanced carcinoma of the cervix.[4] Data from this series suggest that these areas are involved in up to 20% of patients with earlier stages of disease as well. Operative evaluation of these lymph nodes by a transperitoneal approach has been associated with unacceptable morbidity when combined with extended-field radiation therapy.[5, 6] Complications presumably relate to radiation of larger volumes of tissue and to loops of small intestine fixed to incisions in the posterior parietal peritoneum. The extraperitoneal approach to pretreatment evaluation permits excellent access to the pelvic and periaortic lymph nodes, avoids the incision of the posterior peritoneum, and has decreased morbidity while eliminating deaths following extended field irradiation.

Operative evaluation allows modification of radiation therapy by an increase in the dose to an involved pelvic side wall or extension of the field to encompass the periaortic lymph nodes. In a few patients, the detection of widespread intra-abdominal disease has directed therapy toward palliation of bleeding and prevention of ascites rather than cure.

Although operation can be performed safely by an extraperitoneal approach, any accurate, noninvasive method of lymph node evaluation would be highly desirable. Comparison of data obtained by lymphangiogram with results of lymph node biopsies in this series suggests that lymphangiography provides an inaccurate basis on which to modify radiation therapy. Seventy-nine patients, comprising 83% of the treatment series, probably would have benefited from conventional radiation therapy in the absence of operative evaluation. In these patients, total agreement between lymphangiography and lymphadenectomy (64 patients) or disagreement only in the interpretation of the pelvic lymph nodes (15 patients) existed. In 17% of patients, however, treatment based on the results of the lymphangiogram would have been inappropriate. Extended-field radiation therapy applied to all patients in whom the lymphangiogram was C-A positive would have resulted in the overtreatment of seven patients. An additional nine patients in whom the lymphangiogram was C-A negative might have been undertreated on the basis of metastases documented in these areas at the time of operative evaluation. Routine irradiation of

the periaortic region in any patient with a lymphangiogram read as P positive or C-A positive would have appropriately treated 12 and overtreated 20 patients.

The presence of metastases in the common iliac or periaortic lymph nodes was unrelated to clinical stage, cell type, or grade of the primary tumor. Review of postoperative subtraction films provided a basis for a possible false positive correlation of the pelvic lymph nodes in two patients but was not responsible for any discrepancy in the common iliac or periaortic region.

No data are presented to support an increase in the survival of patients managed by this approach. Many patients with metastases to the periaortic lymph nodes also have occult spread to distant sites. An analysis of those patients in whom therapy fails suggest that distant disease, alone or in combination with pelvic recurrence, is present in 52% to 75%.[4, 6] Further documentation of this finding would not obviate the need to evaluate the periaortic lymph nodes but might provide a basis for adjuvant chemotherapy or immunotherapy in patients with extensive lymphatic involvement.

We would like to acknowledge the assistance of James D. Collins, M.D., Department of Radiology, University of California, Los Angeles, Center for the Health Sciences, Sally Shaw, M.D., and John Werner, M.D., Department of Radiology, City of Hope National Medical Center, and Terry Chamorro, R.N.

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Discussion

Dr. David C. Figge, Seattle, Washington. Our current interest in operative staging of cervical cancer was initially stimulated by Nelson in a presentation of 13 such cases before the Society of Gynecologic Oncologists in 1971. The reported inaccuracy of clinical staging was disturbing and has been confirmed by a number of subsequent reports in our literature and by a groupwide protocol study of the gynecologic oncology group. Dr. Lagasse's interesting paper today adds materially to our knowledge of this controversy.

The concept of pretreatment surgical staging in cervical cancer rests on three assumptions. Traditional clinical staging by comparison must be shown to be inaccurate. Treatment modifications must emerge as a result of the surgical procedure and, finally, improved survival is an ultimate goal. Otherwise the increased expense, extended hospitalization, and personal morbidity for the patient are difficult to justify.

In Dr. Lagasse's material, the surgical findings contradicted the clinical staging in one third of the reported cases. In virtually all these cases the disease was more advanced than clinically suspected. Regardless of assigned clinical stage, there was a relatively constant 20% incidence of involved common iliac or aortic node chains. By general agreement such patients should be treated by extended-field radiation directed to the para-aortic area and conventional treatment regimens would be destined to failure in most of these cases.

Any noninvasive technique yielding the same information as surgical staging would be most attractive. Lymphangiography, particularly as supplemented by percutaneous, transperitoneal, fine-needle aspiration of suspicious or positive nodes has been advanced as an alternative. Our essayist reports agreement between the two approaches in only 67% of cases. In 17%, treatment based on the results of a lymphangiogram alone would have been inappropriate. Metastatic nodal disease of less than 0.5 cm in diameter will seldom be detected by lymphangiogram. There is a rather constant 20% false negative result in this diagnostic approach and nodes must be identified as suspicious before fine-needle aspirates are helpful.

Our experience in a rather limited number of patients subjected to pretreatment extraperitoneal node exploration during the past year provides no disagreement. Our first patient was a native Alaskan with early Stage IIB cervical carcinoma. The lymphangiogram was negative. Multiple positive pelvic and paraaortic nodes were confirmed histologically and a subsequent scalene node biopsy was also positive. Our

experience with the lymphangiogram has been most discouraging.

The evidence to date for increased survival by this approach is less than convincing. Reports of long-term survival of patients with positive para-aortic nodes remain mostly anecdotal. Many such patients indeed probably have coincident pelvic recurrence or distant metastases. Often the poor prognosis may reflect, at least in part, the problem of advanced local disease and an overwhelming tumor burden. The prospect may not be all bleak. An interesting recent retrospective study from the New York Medical College reported a limited group of patients with Stage IIB disease arbitrarily treated by extended-field para-aortic radiation. Survival results in this group were significantly higher than in the comparison group treated by conventional fields. Perhaps, as with lymphoma and Hodgkin's disease, we need better to define the patient who may particularly benefit from the findings at staging operation.

This report convincingly recommends the extraperitoneal approach. It appears to be far safer than conventional laparotomy in avoiding the complications that have been reported following radiation. In our patients we have encountered no postirradiation complications to date with this approach. I wonder if Dr. Lagasse would comment further on his preference for the lateral "J" incision. We have found the conventional high, midline incision quite satisfactory, providing that the inferior rectus sheath above the semilunar line is incised laterally from within on both sides.

Dr. William E. Lucas, San Diego, California. Dr. Lagasse has made a significant contribution to our understanding of several aspects of the pattern of spread and diagnosis of lymph node involvement in cervical cancer. This is in addition to a series of studies from the University of California, Los Angeles, under the aegis of Morton. If I am not mistaken, the current President, Dr. Dignam, was involved in some of the earliest of these studies. This is an innovative approach and the lack of morbidity associated with the extraperitoneal approach is a testimony to the acceptability of the technique in skilled hands. The information relating the results of lymphangiography to surgical findings is of considerable value in helping to settle, in the negative, the argument regarding the value of this diagnostic technique in the evaluation of cervical cancer patients. It is our view that if intraperitoneal disease is present, as established by laparoscopy, then lymph node dissection becomes unnecessary. Our protocol is to perform laparoscopy first and then an extraperitoneal para-aortic node dissection via a right periumbilical incision, if there is no intraperitoneal disease. In 20 patients, so far, 25% have had intraperitoneal disease which is much higher than the incidence reported by Dr. Lagasse. These patients have Stage IIB through Stage IV disease. The reasons for carrying out para-aortic and common iliac node sampling are readily appreciated since we need to segregate those patients who, from the outset, will not be cured by conventional radiation fields, because of lymph node involvement at a higher level. These patients become candidates for extended irradiation fields and/or chemotherapy. At our institution, in collaboration with Byfield and Lacey, we are using a protocol which combines irradiation and chemotherapy in all patients who have disease involving the uterus and intraperitoneal structures or para-aortic lymph nodes.

The reasons for doing a pelvic lymphadenectomy are less clear since all these patients are treated with whole-pelvis irradiation, and the pelvic node findings did not significantly alter the treatment plan in 98 of 104 patients. I do not believe that it will be possible, yet, from the design of this study, to learn whether removal of involved pelvic nodes followed by irradiation improves end results, although, this question very much needs to be answered. The converse seems well established, that pelvic lymphadenectomy subsequent to full irradiation increases only morbidity and not cure rate. It is well known that combinations of irradiation and lymphadenectomy increase the incidence of urologic injury and lymphocysts. I would like to ask Dr. Lagasse if, from this study and his previous research into the role of irradiation in sterilizing pelvic lymph nodes containing metastatic cervical cancer, he can develop data which might help us answer the question of whether or not postlymphadenectomy radiation improves survival.

Dr. Ivan I. Langley, Portland, Oregon. I would like to know the amount or the use of left scalene node biopsy as a part of the staging procedure. We have included this and wonder if he has as well.

Dr. Lagasse (Closing). Dr. Figge referred to Sall's cases of Stage IIB carcinoma of the cervix, all of which were treated with periaortic irradiation without prior node biopsies. The 4,500 rads that he used, in the same dosage that we employ, did not cause added complications in his patients. The only complication in the present series that appeared related to extended-field radiation was gastric bleeding in one patient with previous ulcer history.

I believe that staging studies need to be continued so that we will know which patients have spread of disease. Patients with positive common or aortic nodes are possibly at high risk for distant spread and may be candidates for adjuvant chemotherapy. Dr. Figge mentioned that he has performed extraperitoneal lymphadenectomy through a midline incision by peeling the peritoneum free and dissecting behind it. This is an interesting approach which should allow for adequate exposure of the retroperitoneal space.

In answer to Dr. Lucas' question regarding the adequacy of the intraperitoneal exploration, we make a 15 to 20 cm opening in the peritoneum and do a thorough intra-abdominal examination. Tubes and ovaries can be removed through this incision if required by the

presence of abnormality or disease. It is important to detect intraperitoneal metastases when present, and this can be done prior to node removal using the surgical approach we have described. It is not certain if lymphadenectomy itself is therapeutic in patients who have positive nodes. Perhaps removal of very bulky involved nodes will increase the chance of cure with subsequent radiation.

Scalene lymph node biopsies were not done in this series. Metastases to the scalene node may be another indication of systemic disease like the finding of positive periaortic nodes and might indicate which patients should be treated with adjuvant chemotherapy.

Classic pages in
OBSTETRICS AND GYNECOLOGY
Lawrence D. Longo, M.D.

Aberrant portions of the müllerian duct found in an ovary

WILLIAM WOOD RUSSELL
Johns Hopkins Hospital Bulletin, vol. 10, pp. 8-10, 1899

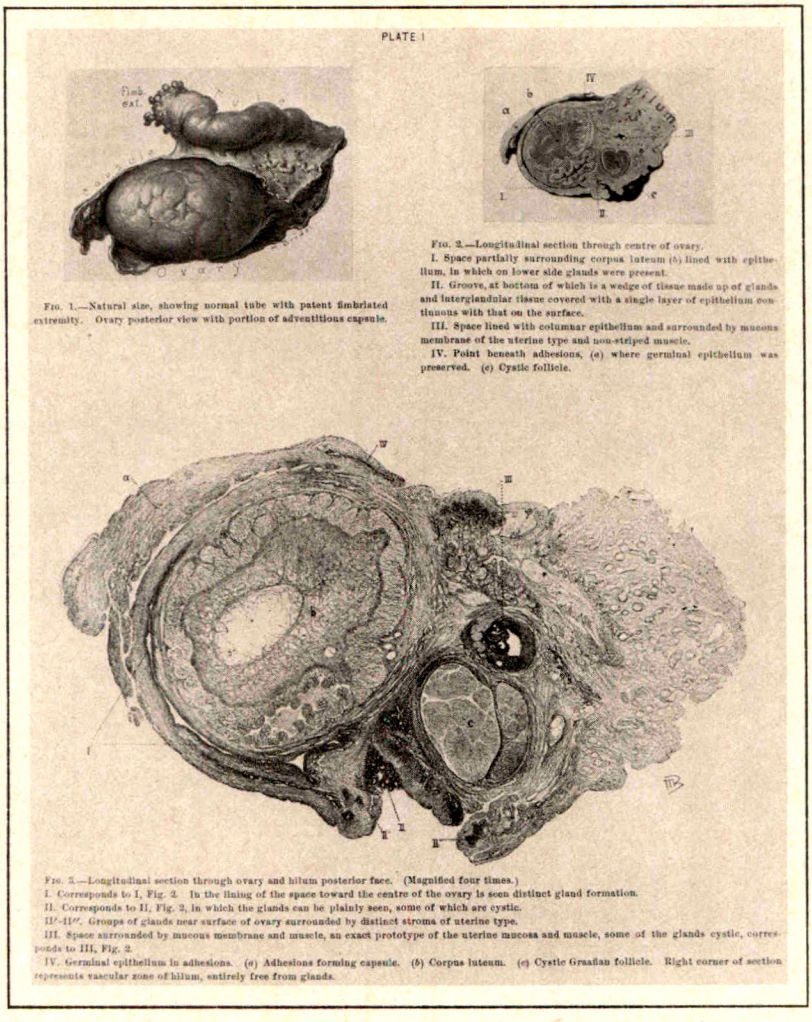


FIG. 1.—Natural size, showing normal tube with patent fimbriated extremity. Ovary posterior view with portion of adventitious capsule.

FIG. 2.—Longitudinal section through centre of ovary.
I. Space partially surrounding corpus luteum (*b*) lined with epithelium, in which on lower side glands were present.
II. Groove, at bottom of which is a wedge of tissue made up of glands and intergiandular tissue covered with a single layer of epithelium continuous with that on the surface.
III. Space lined with columnar epithelium and surrounded by mucous membrane of the uterine type and non-striped muscle.
IV. Point beneath adhesions, (*a*) where germinal epithelium was preserved. (*c*) Cystic follicle.

FIG. 3.—Longitudinal section through ovary and hilum posterior face. (Magnified four times.)
I. Corresponds to I, Fig. 2. In the lining of the space toward the centre of the ovary is seen distinct gland formation.
II. Corresponds to II, Fig. 2, in which the glands can be plainly seen, some of which are cystic.
II′-II″. Groups of glands near surface of ovary surrounded by distinct stroma of uterine type.
III. Space surrounded by mucous membrane and muscle, an exact prototype of the uterine mucosa and muscle, some of the glands cystic, corresponds to III, Fig. 2.
IV. Germinal epithelium in adhesions. (*a*) Adhesions forming capsule. (*b*) Corpus luteum. (*c*) Cystic Graafian follicle. Right corner of section represents vascular zone of hilum, entirely free from glands.

During the latter part of the nineteenth century several writers described pelvic lesions that probably were endometriosis. Carl von Rokitansky may have referred to this entity in his report, "Cystosarcoma adenoides ovarii uterinum" (Lehrb. Pathol. Anat. 3:423, 1861) and Carl Breus used the term "chocolate cyst" in reporting involvement of the uterus and cul-de-sac (Über wahre epithelführende Cystenbildung in Uterus-

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myomen, Leipzig, 1894, F. Deuticke). Russell first reported finding endometrial tissue in the ovaries. Fig. 1 from Plate 1 illustrates the enlarged ovary, while Figs. 2 and 3 demonstrate the foci of endometrial glands and stroma with accompanying smooth muscle. (These figures, incidentally, are from the pen of Max Brödel, the great medical illustrator.) Russell noted: "On microscopic study of the right ovary, we were astonished to find areas which were an exact prototype of the uterine glands and interglandular connective tissue." He described the ovary in detail: "On the posterior surface at a considerable distance from the hilum, was a shallow groove partly filled with glands of the uterine type . . .. In the substance of the ovary . . . was a band of glands imbedded in connective tissue. The glands were arranged as in the normal uterine mucous membrane and opened into the spaces, their epithelium being continuous with its lining membrane. The interglandular connective tissue was composed of small cells with darkly staining oval and round nuclei almost completely filling the cell body, in fact identical with that found in the uterus. Beneath the spaces were bundles of muscle . . .. The whole formed an exact reproduction of a portion of the uterine mucous membrane and muscle." Russell then carefully reviewed the embryology of these tissues and concluded that the aberrant endometrial tissue arose from müllerian duct (paramesonephric) tissue. Robert Meyer argued that metaplasia of celomic membrane gave rise to these lesions (Uber den Stande der Frage der adenomyositis Adenomyome . . ., Zentralbl. Gynaekol. 36:745, 1919). John A. Sampson first coined the term "endometriosis" and explained its histogenesis by "seeding" or implantation from other cysts (Perforating hemorrhagic (chocolate) cysts of the ovary . . ., Arch. Surg. 3:245, 1921). Later Sampson championed the theory of transtubal regurgitation of endometrial fragments during menstruation as the primary cause of this condition (Peritoneal endometriosis, due to menstrual dissemination of endometrial tissue into peritoneal cavity, AM. J. OBSTET. GYNECOL. 14:422, 1927). Russell, with Thomas S. Cullen, a disciple of Howard Kelly, practiced in Baltimore and served as a member of the Department of Gynecology at The Johns Hopkins Hospital. One of the founders of the American College of Surgeons, Russell wrote on many topics of gynecologic interest, including the clinical course of patients with carcinoma of the uterus subsequent to hysterectomy (Johns Hopkins Hosp. Bull. 6:154, 1895) and suprapubic hysterotomy as a means of diagnosis and treatment of diseases of the uterus (Johns Hopkins Hosp. Bull. 17:134, 1906).

COMMUNICATIONS IN BRIEF

This section is suitable for reporting results of therapeutic trials, descriptions of new procedures or instruments, and case reports which illustrate a principle. Reports should be limited to seven hundred words and two references. Use of an illustration or table requires a proportionate reduction in total words.

Association of Legionnaires' disease and pregnancy

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DURING A RECENT epidemic of Legionnaires' disease which occurred in Vermont between May and October of 1977, 32 confirmed and 24 highly probable cases were studied.[1] The majority of cases occurred in patients with chronic underlying diseases such as cancer or chronic bronchitis, in cigarette smokers, and in the immunocompromised host. One of these patients became ill following a cesarean section.

A 29-year-old woman, gravida 2, para 1, was admitted to a regional hospital on July 26, 1977, because of hypertension related to pregnancy. Her last menstrual period was on December 5, 1976, with an estimated date of confinement of September 11, 1977. Hospitalization became necessary because of increasing blood pressure. During the subsequent week of hospitalization there was a 50% fall in estriols and the patient developed a positive oxytocin challenge test (OCT). Evaluation of gestational age by ultrasound was consistent with the patient's dates. An L/S ratio was less than 1:1. She was transferred on August 2, 1977, to the Maternal Fetal Medicine Service at the Medical Center Hospital of Vermont (MCHV).

The patient's blood pressure was stabilized with intravenous Aldomet and a repeat OCT was scheduled. Prior to the OCT, there was the spontaneous development of profound fetal bradycardia necessitating emergency cesarean section. A 2,120 gram male fetus with Apgar scores of 4 and 6 at 1 and 5 minutes, respectively was born. Forty percent abruptio placentae was present. The patient's first few days of postoperative recovery were without complication.

On postoperative day 4 (day 5 after admission to the MCHV) the patient's temperature was 38° C. On postoperative day 5 the patient complained of sudden onset of sharp, bilateral chest pain and shortness of breath. Because of a previous episode of possible phlebitis in 1970 following an ankle injury, pulmonary embolism was suspected. Arterial blood gases revealed a pH of 7.15, Po_2 of 78, and Pco_2 of 30 on room air. A white blood cell count was 14,700, with a normal differential. The initial chest roentgenogram revealed a prominent heart and congestion. No definite evidence of a pneumonia process or pleural effusion was seen. Roentgenograms obtained approximately 16 hours later revealed increased density in the right and left lower lung fields and the presence of a right pleural effusion. This was suggestive of an inflammatory process. Ventilation-perfusion scan was performed in an attempt to clarify the pulmonary process but did not differentiate a pneumonia process from pulmonary emboli. Temperatures spiked at 38.8° C on postoperative day 5 and 38.5° C on postoperative day 6; still the most likely diagnosis was considered to be pulmonary embolism and the patient was begun on intravenous heparin therapy. Clinical and roentgenographic response was very slow. She was discharged on hospital day 16 to be maintained on oral anticoagulation therapy.

A serum specimen was obtained approximately 3 weeks after discharge for determination of indirect fluorescent antibody against Legionnaires' bacterium and was reported to be 1:512. A single serum of 1:256 or greater is considered significant and makes the diagnosis of Legionnaires' disease highly probable.[1]

Since Legionnaires' disease is known to cause more severe disease in the chronically ill and the immunosuppressed host, it is important to suspect the diagnosis as early as possible so that appropriate antibiotic therapy can be started. It is unknown whether pregnancy, which carries with it an increased risk for viral infections, also carries an increased risk for Legionnaires' disease. The case discussed in this report had a clinical picture compatible with Legionnaires' disease:

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sudden onset of undiagnosed pneumonia with granulocytosis, fever, an incubation period of 2 to 10 days, and a pleural effusion. Yet, had there not been a major epidemic of Legionnaires' disease in Vermont and in other states in the northeast at that time, the diagnosis would have been missed. Although it is felt by some that pulmonary embolism is perhaps too often diagnosed and overtreated,[2] our patient did have sudden onset of chest pain with shortness of breath and mild hemoptysis and might well have had both Legionnaires' disease and pulmonary embolism. These latter symptoms have also been described in Legionnaires' disease without evidence of pulmonary embolism, however. In either instance, the addition of erythromycin might have made recovery more rapid.

To our knowledge, this is the first reported association between Legionnaires' disease and pregnancy. The importance and significance of this association is not yet known since total experience with Legionnaires' disease is still very limited. Only an awareness of the possible presence of Legionnaires' disease during pregnancy will lead to an answer to this question as well as to the prompt institution of appropriate therapy.

We thank Dr. Nello Delbel for the referral of this patient.

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Prenatal diagnosis of sacrococcygeal teratoma

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MODERN TECHNIQUES for assessment of fetal malformations include amniocentesis, radiography, amniography, fetography, fetoscopy, and ultrasonography. Perhaps the most valuable and undoubtedly the least hazardous of these techniques is ultrasonography. Hydrocephalus, anencephaly, meningomyelocele, polycystic kidneys, and omphalocele are among the malformations previously diagnosed prenatally by ultrasonography. The following case report documents the prenatal diagnosis of sacrococcygeal teratoma. This diagnosis greatly influenced the subsequent management of the pregnancy.

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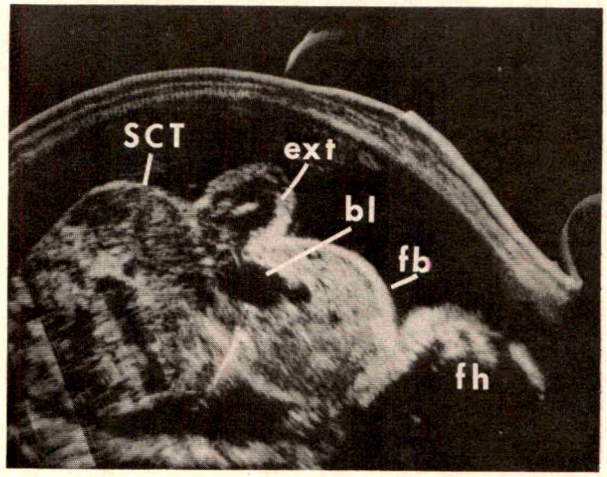


Fig. 1. Ultrasonogram of fetus at 31 weeks' gestation showing large sacrococcygeal teratoma *(SCT). ext,* Lower extremity; *bl,* urinary bladder; *fb,* fetal body; *fh,* fetal head.

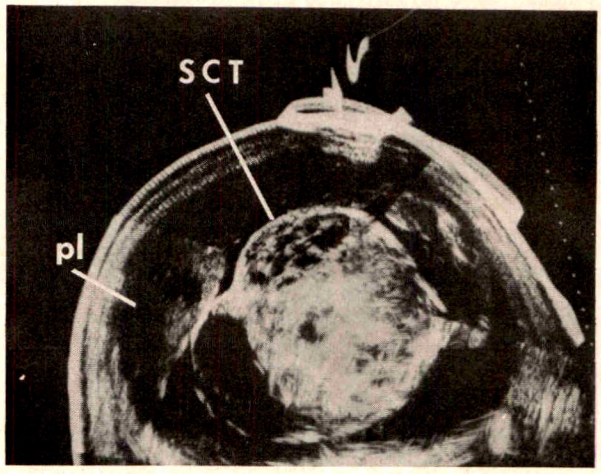


Fig. 2. Ultrasonogram at 31 weeks' gestation showing transverse section through sacrococcygeal teratoma *(SCT).* Bizarre, complex echo pattern with multiple cystic spaces is noted. *pl,* Placenta.

A 29-year-old black woman, gravida 4, para 2, abortus 1, was hospitalized at 31 weeks' gestation because of polyhydramnios and abdominal pain. Her uterine fundal height had increased from 30 to 37 cm during the previous 2 weeks.

Ultrasonography revealed the fetal biparietal diameter and fetal trunk size consistent with 31 weeks' gestation. At the caudal end of the fetal trunk was a complex mass which measured 13 cm in greatest diameter (Figs. 1 and 2). This mass was contiguous with the fetal body. It appeared generally solid, with bizarre internal echoes, but contained multiple cystic areas. No defects were seen in the fetal spine. Distention and subsequent emptying of the fetal urinary bladder were noted. The mass was thought to represent a large sacrococcygeal teratoma. Marked polyhydramnios was present.

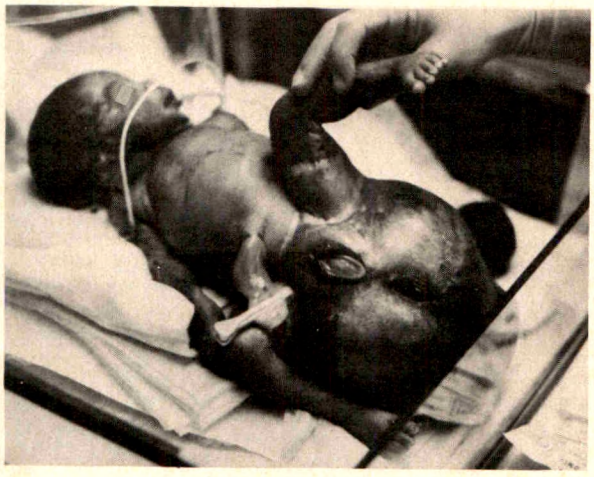


Fig. 3. Premature infant with large sacrococcygeal teratoma. Note forward displacement of anus. Tumor mass comprised 1,450 grams of 2,970 gram birth weight.

Polyhydramnios increased with uterine fundal height reaching 41 cm. Amniocentesis was performed 1 week after hospitalization because of incapacitating abdominal discomfort, and 300 ml of amniotic fluid was withdrawn. This fluid had a lecithin/sphingomyelin (L/S) ratio of 1:2, creatinine concentration of 1.8 mg/dl, and alpha fetoprotein concentration of 0.13 mg/dl. Relief of her discomfort was only partial and temporary. Repeat amniocentesis was necessary 2 days later, at which time 500 ml of fluid were withdrawn without incident. Because of the fear of premature labor, maternal betamethasone was used to induce fetal pulmonary maturity. Premature labor did ensue 2 days after the second amniocentesis. Cesarean section was performed, with delivery of a 2,970 gram female infant. A sacrococcygeal teratoma measuring 14 cm in diameter was present (Fig. 3). No other anomalies were found. The infant developed mild respiratory distress. The tumor was resected 5 days after delivery and weighed 1,450 grams.

Prenatal diagnosis of sacrococcygeal teratoma (SCT) is rare. The tumor most commonly is detected on routine examination of the neonate. However, large tumors may obstruct labor and be suspected on vaginal examination after delivery of the fetal head and upper body. In such cases the infant almost invariably dies before delivery can be completed.

Previous reports of fetal malformations diagnosed by ultrasonography appear to have made the diagnosis of SCT only in retrospect.[1, 2] In none of the three cases previously reported was the diagnosis of SCT used to assist in delivery of a living infant; one of these fetuses died antepartum and the other two died during labor and vaginal delivery.

In the case reported, the presence of polyhydramnios led to ultrasonography. The association between major fetal malformations and polyhydramnios is well known, and the presence of fetal anomaly should be considered in the evaluation of polyhydramnios. The bizarre and complex ultrasonographic characteristics and the location of the fetal tumor in this case were thought to be strongly indicative of SCT. The possibility of lumbosacral meningomyelocele was considered, but careful ultrasonographic examination of the fetal vertebral column showed no suggestion of spina bifida, and the amniotic fluid alpha fetoprotein concentration was within normal limits.

This case report confirms that SCT can be diagnosed prenatally. When such a tumor is diagnosed, the pediatrician and pediatric surgeon can be alerted even prior to delivery, and definitive management can be initiated at the earliest possible opportunity. Cesarean section delivery was elected in this case to prevent both fetal and maternal trauma and to avoid the high rate of perinatal death which accompanies vaginal delivery of such an infant.

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Lidocaine interference in lecithin/sphingomyelin ratios

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LIDOCAINE is commonly used as a local anesthetic for amniocentesis and residual lidocaine may contaminate the amniotic fluid specimen if the same syringe is used for the local anesthetic and the specimen. We found interference in estimating the lecithin/sphingomyelin (L/S) ratio (according to the method of Gluck and Kulovich[1]) of an amniotic fluid contaminated with lidocaine. We report the case and our subsequent investigations of the phenomenon.

An L/S ratio was performed on a woman, gravida 2, para 1, at 37 weeks' gestation who had both anti-C and -D antibodies. The chromatography pattern of the extracted phospholipids could not be interpreted because of an interfering substance which smeared from the sphingomyelin region to the phosphatidyl inositol spot. Initially it had a pink color, but this darkened with further charring. A history of residual lidocaine present in the collecting syringe was elicited.

Lidocaine (as 1% lidocaine hydrochloride) was diluted in water and pH adjusted to give a range of values from 6.0 to 9.5. Lidocaine was added to fresh am-

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Table I. L/S ratios of amniotic fluids, and the same fluid after addition of lidocaine

Initial specimen	*Specimen containing 0.08% lidocaine*
1.4	1.9
1.4	2.1
1.6	2.2
1.0	1.1
1.7	2.1

niotic fluids (pH 7.0 to 7.2) with L/S ratios <2.0. L/S ratio estimations were performed on the aqueous lidocaine solutions and the treated amniotic fluid specimens. Lidocaine was not extracted appreciably from aqueous solutions with a pH <8.5. At pH >8.5 it appeared as a pink spot, turning brown with further heating in the region of lecithin. It was, however, readily extracted from amniotic fluid at pH 7.2. At a level of 0.08% (corresponding to a contamination of 0.25 ml of 1% lidocaine in a 3 ml specimen) the results shown in Table I were observed.

At a level of 0.3%, lidocaine appeared as a smear from the sphingomyelin region to the phosphatidyl inositol area, but mainly in the lecithin region. The smear appeared pink initially, then became brown with further heating. The color change phenomenon was not observed at lower concentrations.

Contamination with lidocaine is a potentially serious source of interference in estimation of L/S ratio according to the method of Gluck and Kulovich,[1] as minimal contamination may convert an immature to a mature result. At this low level its presence would pass undetected and the incorrect result would be issued. Since lidocaine has a pKa of 7.9 and is not extracted from aqueous solution at pH 7.0 to 7.2 (the pH of amniotic fluid), the extraction from amniotic fluid is most likely due to formation of ion pairs with phospholipids.

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CORRESPONDENCE

Fetal hemorrhage following blood samplings and use of vacuum extractor

To the Editors

I have read with interest the case report by Drs. Roberts and Stone (AM. J. OBSTET. GYNECOL. 132:109, 1978). This complication is certainly an unusual one; we never had a case of exsanguination among more than 4,000 consecutive (mostly elective) vacuum extractions of fetuses monitored with a clip electrode fixed to the scalp and from which a micro– blood sample was taken at full dilatation. If the stab wound bleeds rather profusely, we apply pressure through the amnioscope with a tampon. If this measure proves insufficient, an extra clip is applied over the scalp wound. To date, these preventive measures have invariably been successful.

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In vitro fertilization in humans

To the Editors:

The issue addressed in this letter is current and consequently it is circumscribed by emotion and a distinct paucity of data. Notwithstanding these shortcomings the query is: What increase in genetic abnormalities can be expected in human embryos as a result of in vitro fertilization? The scope of our response will be limited to the spermatozoon and an analysis of the potential effect of using ejaculated human spermatozoa for in vitro fertilization.

First recognize that the constancy in human sperm deoxyribonucleic acid (DNA) among gametes of a single ejaculate is highly variable.[1] Here the coefficient of variation ranges from 8.5% to 24.3% with a mean of 13.1%. For bull spermatozoa the coefficient of variation is 10.6%[2] Thus, in a human male subject the number of genetically unbalanced gametes may range between 13 and 41 $\times$ 10^6 cells per ejaculate. If one assumes that the vast majority of these cells are alive and motile and that they take part in fertilization in numbers proportionate to those reaching the egg, regardless of genome balance, which on the basis of evidence[3] from other mammals are reasonable assumptions, then the percentage of recognizable chromosomal aberrations in the human conceptus resulting from fertilization by genetically unbalanced spermatozoa should make up a measurable share of the total, estimated to be approximately 7% of all known pregnancies.[4] Jacobs'[4] estimate is that approximately one third or, stated differently, 2% of all known pregnancies may be effected by genetically unbalanced spermatozoa. Yet the reported genetic variation in spermatozoan DNA among gametes in a human ejaculate averages 13%, approximately six times greater than the estimated chromosomal aberrations in humans effected by genetically unbalanced spermatozoa. This can only mean that either the estimates are incorrect or there is strong selective pressure against spermatozoa harboring unbalanced genomes.

It is likely that the estimated percentage of human chromosomal aberrations effected by genetically unbalanced spermatozoa is incorrect, due in part to unaccounted early embryonic losses,[3] but it is unlikely to be off by a factor of 6. Consequently some selective pressure against genetically unbalanced spermatozoa in an ejaculate must occur. The only possible site where selection could take place is within the female reproductive tract. Although this idea was proposed over a decade ago[5] there has been little scientific effort to test the hypothesis. In the rabbit it has been shown that transport through the female reproductive tract reduces the number of ejaculated diploid spermatozoa by approximately 79%[6] and that oviducal spermatozoa have a fertilization advantage over ejaculated spermatozoa in a heterospermic insemination.[7]

If one assumes the difference between the values for genetic variation in a human ejaculate and the recognizable chromosomal aberrations in the human population results from selection within the female tract and calculates the percent of unbalanced gametes selected against, this value (~85%) is strikingly close to the reported reduction of rabbit diploid spermatozoa. Such a comparison, when based on assumptions, proves nothing but should illustrate the potential increase in genetic anomalies that could result from in vitro fertilization. If female tract selection against male gamete anomalies in the human approaches 80%, then a sixfold increase in the probability of fertilization by a genetically unbalanced sperm in vitro would be expected. Whether or not this is correct is unknown, but it certainly emphasizes that human gamete physiology

must be studied more intensely from a fundamental viewpoint.

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Corticosteroids and respiratory distress syndrome

To the Editors:

I read with interest the article by Morrison and colleagues in the June 15, 1978, issue of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY on corticosteroids and respiratory distress syndrome (RDS). They are to be complimented on the meticulous fashion in which the study was performed; however, there were several points I hope they can clarify.

I noted that the study was performed between the years 1972 and 1975. During this time there was little or no literature discussing the association between length of time of membrane rupture and the development of RDS. Additionally there was nothing in the literature about the association of the use of various β-mimetic agents and acceleration of fetal pulmonary maturity. In Table I of the article, although patients in premature labor in both groups seemed to be equally distributed between treatment and control groups there was no mention of duration of membrane rupture and the distribution of these patients in reference to the length of membrane rupture. Additionally, several patients received isoxsuprine and ritodrine in the study, and no mention of the distribution of these patients between treatment and control groups was made.

Should it turn out that in their study both of these factors were equally distributed between Groups I and II, more validity could be placed on the study. Would Dr. Morrison and colleagues please tell us the above-mentioned distributions?

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Reply to Dr. Myers

To the Editors:

In responding to Dr. Myers' letter concerning our study,[1] we thank him for his critical review. He is correct in stating that the literature is sparse concerning the relationship of RDS to premature rupture of the membranes or the use of beta-sympathomimetic agents. Indeed, there was even less in the literature during the planning phases of our study in 1970 and 1971. Because this was a new area of interest we chose to collect pertinent data on many variables including status of membranes and use of tocolytic drugs.

The length of time of rupture of membranes was unequally distributed between the two groups (Table I). However, the maldistribution shows an *increase* in the number of patients in the control group who had ruptured membranes for a longer period of time. We interpreted these data as demonstrating that ruptured membranes did not statistically *decrease* the incidence of RDS. It is possible, however, that the small sample size obviated this interpretation since other authors with larger series have reported rupture of membranes for greater than 24 to 48 hours to be a positive correlate of lung maturity.[2, 3] We did not report this in our original article, but included it in a subsequent report dealing with the lecithin/sphingomyelin ratio values from these patients.[4] Therefore, rupture of the membranes in our series did not bias the study conclusion that the steroid was effective since, if anything, it would have decreased the incidence of RDS in the control group rather than in the study group.

The use of various tocolytic agents (alcohol, ritodrine, or isoxsuprine) was equally distributed in those patients who were admitted in premature labor *with* or *without* ruptured membranes. Also the use of these drugs was equally distributed between the control and study groups (Table II). While other workers have shown a positive correlation (decrease in RDS),[5, 6] we could not find any influence of the beta-sympathomimetic agents on pulmonary surfactant induction although the numbers were small in each category. Currently, we are assessing the effect of several beta-sympathomimetic drugs on the induction of fetal lung maturity in animals[7] as well as assessing the effects of isoxsuprine on pulmonary surfactant induction in a large clinical trial.[8]

Hopefully, continued investigation in this field will lead to the elucidation of the two points raised by Dr.

Table I. Duration of premature ruptured membranes*

Group	Duration		
	<24 hr.	*24-48 hr.*	*>48 hr.*
Treatment Group I	12	5	7
Control Group II	5	8	10

*Duration prior to delivery.

Table II. Tocolytic therapy

Group	Therapy			
	None	*10% alcohol*	*Isoxsuprine*	*Ritodrine*
Treatment Group I	5	24	5	2
Control Group II	3	22	7	1

Myers. As to the validity placed on our study, I am afraid that these two questions, although answered, will not contribute to that end. Only a large comprehensive trial such as the one being conducted by the National Heart, Lung and Blood Institute will assess: (1) the advisability of the use of steroids in a patient at risk for premature delivery, (2) the potential short-term hazards of steroids for mother and fetus, and (3) most importantly, the long-range sequelae, if any, to the infant. Hopefully, answers to these issues will be forthcoming in the near future.

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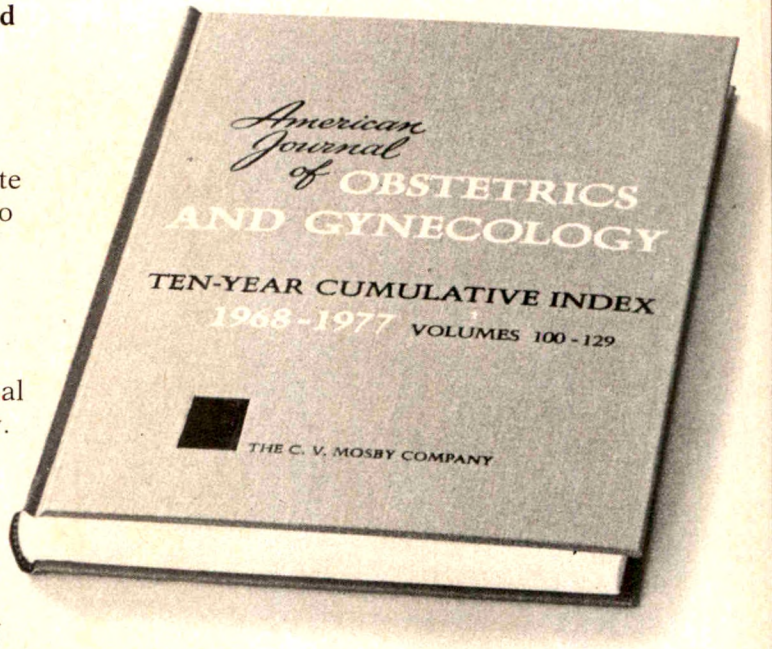
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The Vertebrate Ovary. Edited by Richard E. Jones. 853 pages, illustrated. New York, 1978, Plenum Press. $69.50

The Women's Health Movement. Sheryl Burt Ruzek. 350 pages. New York, 1978, Praeger Publishers, Inc. No price listed.

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While every precaution is taken to insure accuracy, we cannot guarantee against the possibility of an occasional change or omission in the preparation of this index.

Flagyl® (metronidazole) 250 mg.

Warning
Metronidazole has been shown to be carcinogenic in mice and possibly carcinogenic in rats. (See *Warnings*.) Unnecessary use of the drug should be avoided. Its use should be reserved for the conditions described in the *Indications* section.

Indications: For the treatment of symptomatic trichomoniasis in both females and males when the presence of the trichomonad has been confirmed by appropriate laboratory procedures (wet smears and/or cultures). Also for the treatment of asymptomatic females when the organism is associated with endocervicitis, cervicitis, or cervical erosion. *T. vaginalis* infection is a venereal disease and therefore, asymptomatic sexual partners of infected patients should be treated simultaneously if the organism is present. The decision to treat an asymptomatic male partner who has a negative culture or smear, or one in whom no culture has been attempted, is an individual one. In any event, the consort should be treated with Flagyl in cases of reinfection. Flagyl is also indicated for acute intestinal amebiasis (amebic dysentery) and for amebic liver abscess.

Contraindications: Evidence or history of blood dyscrasia, active organic disease of the CNS, the first trimester of pregnancy and a hypersensitivity to metronidazole.

Warnings: Flagyl should not be used in the first trimester of pregnancy (see *Contraindications*). Use with discretion during the second and third trimesters of pregnancy and restrict to those pregnant patients not cured by topical measures. Flagyl (metronidazole) is secreted in the breast milk of nursing mothers. It is not known whether this can be injurious to the newborn. If used during lactation, an alternative method of feeding may be elected.

Note: Tumorigenicity Studies in Rodents. Metronidazole has shown evidence of tumorigenic activity in a number of studies involving chronic, oral administration in mice and rats.

Most prominent among the effects in the mouse was the promotion of pulmonary tumorigenesis. This has been observed in all five reported studies in that species, including one study in which the animals were dosed on an intermittent schedule (administration during every fourth week only). The published results of one of the mouse studies indicate increases in the incidence of malignant lymphomas as well as pulmonary neoplasms associated with lifetime feeding of the drug. All these effects are statistically significant.

Two long-term toxicity studies in the rat have been completed. There was a statistically significant increase in the incidence of various neoplasms, particularly mammary tumors, among female rats administered metronidazole over that noted in the concurrent female control groups.

Two lifetime tumorigenicity studies in hamsters have been performed and reported to be negative.

Metronidazole has been reported to potentiate the anticoagulant effect of coumarin and warfarin resulting in a prolongation or prothrombin time. This possible drug interaction should be considered when Flagyl is prescribed for patients on this type of anticoagulant therapy.

Precautions: Mild leukopenia has been reported during Flagyl use; total and differential leukocyte counts are recommended before and after treatment with the drug, especially if a second course is necessary. Avoid alcoholic beverages during Flagyl therapy because abdominal cramps, nausea, vomiting, headaches and flushing may occur. Discontinue Flagyl promptly if abnormal neurologic signs occur. Exacerbation of moniliasis may occur. In amebic liver abscess, aspirate pus during metronidazole therapy.

Adverse Reactions: Nausea, headache, anorexia, vomiting, diarrhea, epigastric distress, abdominal cramping, constipation, a metallic, sharp and unpleasant taste, furry tongue, glossitis and stomatitis possibly associated with a sudden overgrowth of *Candida*, exacerbation of vaginal candidiasis, an occasional reversible moderate leukopenia, dizziness, incoordination and ataxia, numbness or paresthesia of an extremity, fleeting joint pains, confusion, irritability, depression, insomnia, mild erythematous eruptions, "weakness," urticaria, flushing, nasal congestion, dryness of the mouth, vagina or vulva, pruritus, dysuria, cystitis, a sense of pelvic pressure, dyspareunia, fever, polyuria, incontinence, decrease of libido, proctitis, pyuria and darkened urine have occurred in patients receiving the drug. Patients receiving Flagyl may experience abdominal distress, nausea, vomiting, flushing or headache if alcoholic beverages are consumed. The taste of alcoholic beverages may also be modified. Flattening of the T-wave may be seen in ECG tracings.

Dosage and Administration: ***For Trichomoniasis:*** The recommended dosage for both male and female is one 250-mg. tablet orally three times daily for seven days. When repeat courses of the drug are required, it is recommended that an interval of 4 to 6 weeks elapse between courses and that the presence of the trichomonad be reconfirmed by appropriate laboratory measures. Total and differential leukocyte counts should be made before, during and after retreatment. The male consort should be treated in any event in cases of reinfection.

For Amebiasis: *Adults:* For acute intestinal amebiasis, 750 mg. orally three times daily for 5 to 10 days.

For amebic liver abscess: *Adults:* 500 mg. or 750 mg. orally three times daily for 5 to 10 days.

Children: 35 to 50 mg./kg. of body weight/24 hours, divided into three doses, orally for 10 days.

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Please see adjacent page for brief summary of prescribing information



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Riboflavin, mg.	3.0	150
Niacin, mg.	20	100
Vitamin B_6, mg.	10.0	400
Vitamin B_{12}, mcg.	8	100
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Today's t_ _nag_r exp_ _cts a lot more than medicine from her doctor.

The plight of today's teenager in these socially turbulent times is often precarious at best. According to a recent national survey, there has been a 30% increase in teenage sexual activity in the last five years.[1] Also, half of all out-of-wedlock births are attributed to teens. Up to two-thirds of these are unwanted, unplanned births.[2] Trapped in the midst of rapidly changing sexual mores, the teenager is further beset by uncertainty, timidity, ignorance, and misinformation.

That's why today's younger patient needs and deserves thorough counseling — underlined by compassion, reassurance, and trust — in many areas. These range from the basic facts of life, in some cases, to more serious subjects like venereal disease. But, no issue is more sensitive, or more in need of physician/patient exploration than that of contraception.

Today, contraceptive counseling often culminates in the selection of a low-dose oral contraceptive like Brevicon. Brevicon offers a rate of efficacy comparable to higher-dose formulations and its incidence of menstrual irregularities is low. In 16,345 cycles among 1,168 patients, there were 0.22 pregnancies per 100 woman years. Breakthrough bleeding occurred in 5.1% of cycles, and amenorrhea in 1.0% of cycles. Dropout rate due to menstrual irregularities during the crucial first three months was 3.4%.

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1. Zelnik, M. and Kantner, R.: Sexual and Contraceptive Experience of Young Married Women in the United States, 1976 and 1971. Family Planning Perspectives. Vol. 9, No. 2, March/April 1977.

2. Monthly Vital Statistics Report: Natality Statistics, National Center for Health Statistics, Vol. 26, No. 5, September 1977.

Note: Serious as well as minor side effects have been reported following the use of all oral contraceptives. These include thromboembolic disease. The physician should remain alert to the earliest manifestations of any symptoms of serious disease and discontinue oral contraceptive therapy when appropriate. The physician should be fully aware of the prescribing information for this product.

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ORAL CONTRACEPTIVE (O.C.) AGENTS

INDICATIONS O.C.s are indicated for the prevention of pregnancy. The drop-out rate for medical reasons, as observed in the clinical trials conducted with BREVICON, appears to be somewhat higher than observed with higher dose combination products. The dropout rate due to menstrual disorders and irregularities was also somewhat higher, dropouts being equally split between menstrual disorders and irregularities and other medical reasons attributable to the drug. *DOSE-RELATED RISK OF THROMBOEMBOLISM FROM O.C.s.* Studies have shown a positive association between the dose of estrogens in O.C.s and the risk of thromboembolism. For this reason, it is prudent and in keeping with good principles of therapeutics to minimize exposure to estrogen. The O.C. product prescribed for any given patient should be that product which contains the least amount of estrogen that is compatible with an acceptable pregnancy rate and patient acceptance. It is recommended that new acceptors of O.C.s should be started on preparations containing 0.05 mg or less of estrogen.

CONTRAINDICATIONS 1. Known or suspected pregnancy (see Warning No. 5). 2. O.C.s should not be used in women who have or have had any of the following conditions: a. Thrombophlebitis or thromboembolic disorders. b. Cerebral vascular or coronary artery disease. c. Markedly impaired liver function. d. Known or suspected carcinoma of the breast. e. Known or suspected estrogen dependent neoplasia. f. Undiagnosed abnormal genital bleeding.

WARNINGS: Cigarette smoking increases the risk of serious cardiovascular side effects from O.C. use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use O.C.s should be strongly advised not to smoke.

The use of O.C.s is associated with increased risk of several serious conditions including thromboembolism, stroke, myocardial infarction, liver tumor, gall bladder disease, visual disturbances, fetal abnormalities, and hypertension. Practitioners prescribing O.C.s should be familiar with the following information relating to these risks.

1. *Thromboembolic Disorders and Other Vascular Problems:* An increased risk of thromboembolic and thrombotic disease associated with the use of O.C.s is well established. One British study demonstrated an increased relative risk for fatal venous thromboembolism; two British and three American studies demonstrated an increased relative risk for non-fatal venous thromboembolism. These studies estimate that users of O.C.s are 4 to 11 times more likely than nonusers to develop these diseases without evident cause. CEREBROVASCULAR DISORDERS. Two American studies demonstrated an increased relative risk for stroke, which had not been shown in prior British studies. In a collaborative American study of cerebrovascular disorders in women with and without predisposing causes, it was estimated that the relative risk of hemorrhagic stroke was 2.0 times greater in users than nonusers and the relative risk of thrombotic stroke was 4 to 9.5 times greater in users than in nonusers. A British long-term, follow-up study reported in 1976 a highly significant association between O.C. use and stroke. Another British long-term, follow-up study had suggested such an association in 1974, but the number of cases was too small to estimate the risk. MYOCARDIAL INFARCTION. An increased relative risk of myocardial infarction associated with the use of O.C.s has been reported, confirming a previously suspected association. One study conducted in the United Kingdom found, as expected, that the greater the number of underlying risk factors for coronary artery disease (cigarette smoking, hypertension, hypercholesterolemia, obesity, diabetes, history of preeclamptic toxemia) the higher the risk of developing myocardial infarction, regardless of whether the patient was an O.C. user or not. O.C.s, however, were found to be an additional risk factor. In terms of relative risk, it has been estimated that O.C. users who do not smoke (smoking is considered a major predisposing condition to myocardial infarction) are about twice as likely to have a fatal myocardial infarction as nonusers who do not smoke. O.C. users who are also smokers have about a 5-fold increased risk of fatal infarction compared to users who do not smoke, and about a 10- to 12-fold increased risk compared to nonusers who do not smoke. Furthermore, the number of cigarettes smoked is also an important factor. In determining the importance of these relative risks, however, the baseline rates for various age groups must be given serious consideration. (The estimates are based on British vital statistics which show acute myocardial infarction death rates 2- to 3-times less than in the U.S. for women in these age groups; consequently, actual U.S. death rates could be higher.) The importance of other predisposing conditions mentioned above in determining relative and absolute risks has not been quantified; other synergistic actions may exist. RISK OF DOSE. In an analysis of data derived from several national adverse reaction reporting systems, British investigators concluded that the risk of thromboembolism including coronary thrombosis is directly related to the dose of estrogen used in O.C.s. Preparations containing 0.1 mg or more of estrogen were associated with a higher risk of thromboembolism than those containing 0.05-0.08 mg of estrogen. Their analysis did suggest, however, that the quantity of estrogen may not be the sole factor involved. This finding has been supported by a study in the United States. Careful epidemiological studies to determine the degree of thromboembolic risk associated with progestogen-only O.C.s have not been performed. Cases of thromboembolic disease have been reported in women using these products, and they should not be presumed to be free of excess risk. ESTIMATE OF EXCESS MORTALITY FROM CIRCULATORY DISEASE. A large British prospective study estimated the mortality rate per 100,000 women per year from diseases of the circulatory system for users and nonusers of O.C.s according to age, smoking habits, and duration of use. The overall excess death rate annually from circulatory diseases for O.C. users was estimated to be 20 per 100,000 (ages 15-34—5/100,000; ages 35-44—33/100,000; ages 45-49—140/100,000). The risk is concentrated in older women, in those with a long duration of use, and in cigarette smokers, and may persist after discontinuation of O.C. use. It was not possible, however, to examine the interrelationships of age, smoking, and duration of use, nor to compare the effects of continuous vs. intermittent use. Although the study showed a 10-fold increase in death due to circulatory diseases in users for 5 or more years, all of these deaths occurred in women 35 or older. Until larger numbers of women under 35 with continuous use for 5 or more years are available, it is not possible to assess the magnitude of the relative risk for this younger age group. The available data from a variety of sources have been analyzed to estimate the risk of death associated with various methods of contraception. The estimates of risk of death for each method include the combined risk of the contraceptive method (e.g., thromboembolic and thrombotic disease in the case of O.C.s) plus the risk attributable to pregnancy or abortion in the event of method failure. This latter risk varies with the effectiveness of the contraceptive method. The findings of this analysis are shown in Table 1 below. The study concluded that the mortality associated with all methods of birth control is low and below that of childbirth, with the exception of O.C.s in women over 40 who smoke. (The rates given for pill only/smokers for each age group are for smokers as a class. For "heavy" smokers (more than 15 cigarettes a day), the rates given would be about double; for "light" smokers (less than 15 cigarettes a day), about 50 percent.) The lowest mortality is associated with the condom or diaphragm backed up by early abortion. The study also concluded that O.C. users who smoke, especially those over the age of 30, have a greater mortality risk than O.C. users who do not smoke.

TABLE 1. *The annual number of deaths associated with control of fertility and no control per 100,000 nonsterile women by regimen of control and age of women are:*

	15-19	20-24	25-29	30-34	35-39	40-44
No method	5.6	6.1	7.4	13.9	20.8	22.6
Abortion only	1.2	1.6	1.8	1.7	1.9	1.2
Pill only—nonsmokers	1.3	1.4	1.4	2.2	4.5	7.1
Pill only—smokers	1.5	1.6	1.6	10.8	13.4	58.9
IUDs only	0.9	1.0	1.2	1.4	2.0	1.9
Traditional contraception only	1.1	1.6	2.0	3.6	5.0	4.2
Traditional contraception and abortion	0.2	0.2	0.3	0.3	0.3	0.2

The risk of thromboembolic and thrombotic disease associated with O.C.s [illegible] increased by hypertension, hypercholesterolemia, obesity, diabetes, or history of preeclamptic toxemia and especially by cigarette smoking. Based on the data currently available, the following table gives a gross estimate of the risk of death from circulatory disorders associated with the use of O.C.s:

TABLE 2. *Smoking habits and other predisposing conditions – risk associated with use of O.C.s*

Age	Below 30	30-39	40+
Heavy smokers	C	B	A
Light smokers	D	C	B
Nonsmokers (No predisposing conditions)	D	C,D	C
Nonsmokers (other predisposing conditions)	C	C,B	B,A

A—Use associated with very high risk. C—Use associated with moderate risk.
B—Use associated with high risk. D—Use associated with low risk.

The physician and the patient should be alert to the earliest manifestations of thromboembolic and thrombotic disorders (e.g., thrombophlebitis, pulmonary embolism, cerebrovascular insufficiency, coronary occlusion, retinal thrombosis, and mesenteric thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately. A four- to six-fold increased risk of post-surgery thromboembolic complications has been reported in O.C. users. If feasible, O.C.s should be discontinued at least 4 weeks before surgery of a type associated with an increased risk of thromboembolism or prolonged immobilization. Among patients with thromboembolic disease, the results of retrospective studies suggest the possibility of an increased risk for users who are of blood types A, B, or AB, as compared with those of type O. *Ocular Lesions:* There have been reports of neuro-ocular lesions such as optic neuritis or retinal thrombosis associated with the use of O.C.s. Discontinue O.C. medication if there is unexplained, sudden or gradual, partial or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal vascular lesions; and institute appropriate diagnostic and therapeutic measures. *Carcinoma:* Long-term continuous administration of either natural or synthetic estrogen in certain animal species increases the frequency of certain adenomas, benign or malignant, such as those of the breast, cervix, vagina, uterus, ovary, pituitary and liver. Certain synthetic progestogens, none currently contained in O.C.s, have been noted to increase the incidence of mammary nodules, benign and malignant, in dogs. Several retrospective case-control studies have reported an increased relative risk (3.1 to 13.9 times) associating endometrial carcinoma with the prolonged use of estrogens in postmenopausal women who took estrogen replacement medication to relieve menopausal symptoms. One publication reported on the first 30 cases submitted by physicians to a registry of cases of adenocarcinoma of the endometrium in women under 40 on O.C.s. Of the adenocarcinomas found in women without predisposing risk factors for adenocarcinoma of the endometrium (e.g., irregular bleeding at the time O.C.s were first given, polycystic ovaries) nearly all occurred in women who had used a sequential O.C. These products are no longer marketed. No statistical association has been reported suggesting an increased risk of endometrial cancer in users of conventional combination or progestogen-only O.C.s, although individual cases have been reported. Several studies have shown no increased risk of breast cancer to women taking O.C.s or estrogens. In one study, however, while no overall increased risk of breast cancer was noted in women treated with O.C.s, a greater risk was suggested for the subgroups of O.C. users with documented benign breast disease and for long-term (2-4 years) users. One other study indicated an increasing risk of breast cancer in women taking menopausal estrogens, which increased with duration of follow-up. A reduced occurrence of benign breast tumors in users of O.C.s has been well documented. In a prospective study of women with cervical dysplasia, there was an increase in severity and of conversion to cancer *in situ* in O.C. users compared with nonusers. This became statistically significant after 3 to 4 years of use. Nonreversal of dysplasia within the first 6 months of pill use was suggested to be predictive of progression after prolonged exposure. There have been other reports of microglandular hyperplasia of the cervix in users of O.C.s. In summary, there is at present no confirmed evidence from human studies of an increased risk of cancer associated with O.C.s. Close clinical surveillance of all women taking O.C.s is, nevertheless, essential. In all cases of undiagnosed persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be taken to rule out malignancy. Women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease or abnormal mammograms should be monitored with particular care if they elect to use O.C.s instead of other methods of contraception. 4. *Liver Tumors:* Sudden severe abdominal pain or shock may be due to rupture and hemorrhage of a liver tumor. There have been reports associating benign or malignant liver tumors with O.C. use. This has been reported in short-term as well as long-term users of O.C.s. One study showed that O.C. formulations with high hormonal potency were associated with a higher risk than lower potency formulations. Two studies relate risk with duration of use, the risk being much greater after 4 or more years of use. Although it is an uncommon lesion, it should be considered in women presenting with an "acute abdomen". The tumor may cause serious or fatal hemorrhage. Patients with liver tumors have demonstrated variable clinical features which may make preoperative diagnosis difficult. Some cases presented because of right upper quadrant masses, while most had signs and symptoms of acute intraperitoneal hemorrhage. Routine radiological and laboratory studies may not be helpful. Liver scans may clearly show a focal defect. Hepatic arteriography may be a useful procedure in diagnosing primary liver neoplasm. 5. *Use in or Immediately Preceding Pregnancy, Birth Defects in Offspring, and Malignancy in Female Offspring:* The use of female sex hormones—both estrogenic and progestational agents—during early pregnancy may seriously damage the offspring. It has been shown that females exposed *in utero* to diethylstilbestrol, a nonsteroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare. This risk has been estimated to be of the order of 1 in 1,000 exposures or less. Although there is no evidence at the present time that O.C.s further enhance the risk of developing this type of malignancy, such patients should be monitored with particular care if they elect to use O.C.s instead of other methods of contraception. Furthermore, a high percentage of women exposed to diethylstilbestrol (from 30 to 90%) have been found to have epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether this condition is a precursor of vaginal malignancy. Male children so exposed may develop abnormalities of the urogenital tract. Although similar data are not available with the use of other estrogens, it cannot be presumed that they would not induce similar changes. An increased risk of congenital anomalies, including heart defects and limb defects, has been reported following use of sex hormones, including O.C.s, in pregnancy. In one case-control study it was estimated that there was a 4.7-fold increased relative risk of limb-reduction defects in infants exposed *in utero* to sex hormones (O.C.s, hormonal withdrawal tests for pregnancy or attempted treatment for threatened abortion). Some of these exposures were very short and involved only a few days of treatment. The data suggest that the risk of limb-reduction defects in exposed fetuses is somewhat less than 1 in 1,000 live births. In a large prospective study, cardiovascular defects in children born to women who received female hormones, including O.C.s, during early pregnancy occurred at a rate of 18.2 per 1,000 births, compared to 7.8 per 1,000 for children not so exposed *in utero*. These results are statistically significant. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well controlled studies that progestogens are effective for these uses. There is some evidence that triploidy and possibly other types of polyploidy are increased among abortuses from women who become pregnant soon after ceasing O.C.s. Embryos with these anomalies are virtually always aborted spontaneously. Whether there is an overall increase in spontaneous abortion of pregnancies conceived soon after stopping O.C.s is unknown. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at the time of the first missed period (or after 45 days from the last menstrual period if progestogen-only O.C.s are used) and further use of O.C.s should be withheld until pregnancy has been ruled out. It is recommended that for any patient who has missed two consecutive periods, pregnancy should be ruled out before continuing the contraceptive regimen. If pregnancy is confirmed, the patient should be apprised of the potential risks to the fetus and the advisability of continuation of the pregnancy should be discussed in the light of these risks. It is also recommended that women who discontinue O.C.s with the intent of becoming pregnant use an alternate form of contraception for a period of time before attempting to conceive. Many clinicians recommend 3 months, although no precise information is available on which to base this recommendation. 6. *Gall Bladder Disease:* Studies report an increased risk of gall bladder disease in users of O.C.s or estrogens. In one study, an increased risk appeared after 2 years of use and doubled after 4 or 5 years of use. In another study an increased risk was apparent between 6 and 12 months of use. 7. *Carbohydrate and Lipid Metabolic Effects:* A decrease in glucose tolerance has been observed in a significant percentage of patients on O.C.s. For this reason, prediabetic and diabetic patients should be carefully observed while receiving O.C.s. An increase in triglycerides and total phospholipids has been observed in patients receiving O.C.s. The clinical significance of this finding is unknown. 8. *Elevated Blood Pressure:* An increase in blood pressure has been reported with O.C. use. In some women, hypertension may occur within a few months of beginning O.C. use. In the first year of use, the prevalence of women with hypertension is low in users and may be no higher than that of a comparable group of nonusers. The prevalence in users increases, however, with longer exposure, and in the fifth year of use is two and a half to three times the reported prevalence in the first year. Age is also strongly correlated with the development of hypertension in O.C. users. Women with a history of elevated blood pressure (hypertension), preexisting renal disease, a history of toxemia or elevated blood pressure during pregnancy, a familial tendency to hypertension or its consequences, or a history of excessive weight gain or fluid retention during the menstrual cycle may be more likely to develop elevation of blood pressure when given O.C.s and therefore, should be monitored closely. Even though elevated blood pressure may remain within the "normal" range, the clinical implications of elevations should not be ignored and close surveillance is indicated, particularly for women with other risk factors for cardiovascular disease or stroke. High blood pressure may or may not persist after discontinuation of the O.C. 9. *Headache:* The onset or exacerbation of migraine or development of headache of a new pattern which is recurrent, persistent, or severe, requires discontinuation of O.C.s and evaluation of the cause. 10. *Bleeding Irregularities:* Breakthrough bleeding, spotting, and missed menses are frequent reasons for patients discontinuing O.C.s. In breakthrough bleeding, as in all cases of irregular bleeding from the vagina, nonfunctional causes should be borne in mind. In undiagnosed persistent or recurrent abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy. If pathology has been excluded, time or a change to another formulation may solve the problem. Changing to an O.C. with a higher estrogen content, while potentially useful in minimizing menstrual irregularity should be done only if necessary since this may increase the risk of thromboembolic disease. Women with a past history of oligomenorrhea or secondary amenorrhea or young women without regular cycles may have a tendency to remain anovulatory or to become amenorrheic after discontinuation of O.C.s. Women with these preexisting problems should be advised of this possibility and encouraged to use other contraceptive methods. Post-use anovulation, possibly prolonged, may also occur in women without previous irregularities. A higher incidence of galactorrhea and of pituitary tumors (e.g., adenomas) has been associated with amenorrhea in former users compared with nonusers. One study reported a 16-fold increased prevalence of pituitary prolactin-secreting tumors among patients with postpill amenorrhea when galactorrhea was present. 11. *Infertility:* There is evidence of impairment of fertility in women discontinuing O.C.s in comparison with those discontinuing other methods of contraception. The impairment appears to be independent of the duration of use of the preparations. While the impairment diminishes with time, there is still an appreciable difference in the results in nulliparous women for the O.C. and non-O.C. groups 30 months after discontinuation of birth control. For parous women the difference is no longer apparent 30 months after cessation of contraception. 12. *Ectopic Pregnancy:* Ectopic as well as intrauterine pregnancy may occur in contraceptive failures. However, in progestogen-only O.C. failures, the ratio of ectopic to intrauterine pregnancies is higher than in women who are not receiving O.C.s, since the drugs are more effective in preventing intrauterine than ectopic pregnancies. 13. *Breast Feeding:* O.C.s given in the postpartum period may interfere with lactation. There may be a decrease in the quantity and quality of the breast milk. Furthermore, a small fraction of the hormonal agents in O.C.s has been identified in the milk of mothers receiving these drugs. The effects, if any, on the breast fed child have not been determined. If feasible, the use of O.C.s should be deferred until the infant has been weaned. **PRECAUTIONS** *GENERAL* 1. A complete medical and family history should be taken prior to the initiation of O.C.s. The pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen and pelvic organs, including Papanicolaou smear and relevant laboratory tests. As a general rule, O.C.s should not be prescribed for longer than 1 year without another physical examination being performed. 2. Under the influence of estrogen-progestogen preparations, preexisting uterine leiomyomata may increase in size. 3. Patients with a history of psychic depression should be carefully observed and the drug discontinued if depression recurs to a serious degree. Patients becoming significantly depressed while taking O.C.s should stop the medication and use an alternate method of contraception in an attempt to determine whether the symptom is drug related. 4. O.C.s may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention, such as convulsive disorders, migraine syndrome, asthma or cardiac, hepatic or renal insufficiency. 5. Patients with a past history of jaundice during pregnancy have an increased risk of recurrence of jaundice while receiving O.C. therapy. If jaundice develops in any patient receiving such drugs, the medication should be discontinued. 6. Steroid hormones may be poorly metabolized in patients with impaired liver function and should be administered with caution in such patients. 7. O.C. users may have disturbances in normal tryptophan metabolism which may result in a relative pyridoxine deficiency. The clinical significance of this is unknown. 8. Serum folate levels may be depressed by O.C. therapy. Since the pregnant woman is predisposed to the development of folate deficiency and the incidence of folate deficiency increases with increasing gestation, it is possible that if a woman becomes pregnant shortly after stopping O.C.s, she may have a greater chance of developing folate deficiency and complications attributed to this deficiency. 9. The pathologist should be advised of O.C. therapy when relevant specimens are submitted. 10. Certain endocrine and liver function tests and blood components may be affected by estrogen-containing O.C.s. For example: a. Increased sulfobromophthalein retention. b. Increased prothrombin and factors VII, VIII, IX and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability. c. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG, free T4 concentration is unaltered. d. Decreased pregnanediol excretion. e. Reduced response to metyrapone test. *DRUG INTERACTIONS* O.C.s may be rendered less effective by virtue of drug interaction with rifampin, isoniazid, ampicillin, neomycin, penicillin, chloramphenicol, sulfonamides, nitrofurantoin, barbiturates, phenytoin, primidone, analgesics, tranquilizers and antimigraine preparations. O.C.s may alter the effectiveness of other types of drugs, such as oral anticoagulants, anticonvulsants, tricyclic antidepressants, antihypertensive agents (e.g., quanethidine), vitamins and hypoglycemic agents. *CARCINOGENESIS* See Warnings. *PREGNANCY* Pregnancy category X. See Contraindications and Warnings. *NURSING MOTHERS* See Warnings. **ADVERSE REACTIONS** An increased risk of the following serious adverse reactions has been associated with the use of O.C.s (see Warnings): thrombophlebitis, thrombosis, pulmonary embolism, coronary thrombosis, cerebral thrombosis, mesenteric thrombosis, liver tumors, cerebral hemorrhage, hypertension, gall bladder disease, congenital anomalies, neuro-ocular lesions, e.g., retinal thrombosis or optic neuritis. The following adverse reactions have been reported in patients receiving O.C.s and are believed to be drug related: bleeding irregularities (breakthrough bleeding, spotting, missed menses during treatment, amenorrhea after treatment), gastrointestinal symptoms (nausea, vomiting, bloating, abdominal cramps), dysmenorrhea, infertility after discontinuation of treatment, edema, chloasma or melasma which may persist after drug is discontinued, breast changes (tenderness, enlargement, and secretion), intolerance to contact lenses, change in corneal curvature (steepening) change in weight (increase or decrease), change in cervical erosion and cervical secretion, possible diminution in lactation when given immediately postpartum, premenstrual jaundice, migraine, increase in size of uterine leiomyomata, rash (allergic), mental depression, reduced tolerance to carbohydrates, vaginal candidiasis, prolactin-secreting pituitary tumors. The following adverse reactions have been reported in users of O.C.s, and the association has neither confirmed nor refuted: premenstrual-like syndrome, cataracts, changes in libido, chorea, changes in appetite, cystitis-like syndrome, headache, dizziness, hirsutism, loss of hair, erythema multiforme, erythema nodosum, hemorrhagic eruption, vaginitis, porphyria, impaired renal function. **INFORMATION FOR THE PATIENT** (See Patient Package Insert)

Destroys Trichomonads in 15 seconds

Immediate symptomatic relief

In vitro studies[1,2] show that within 15 seconds of contact, VAGISEC Douche permeates the trichomonad's outer membrane and weakens its cell wall, causing it to swell and die.

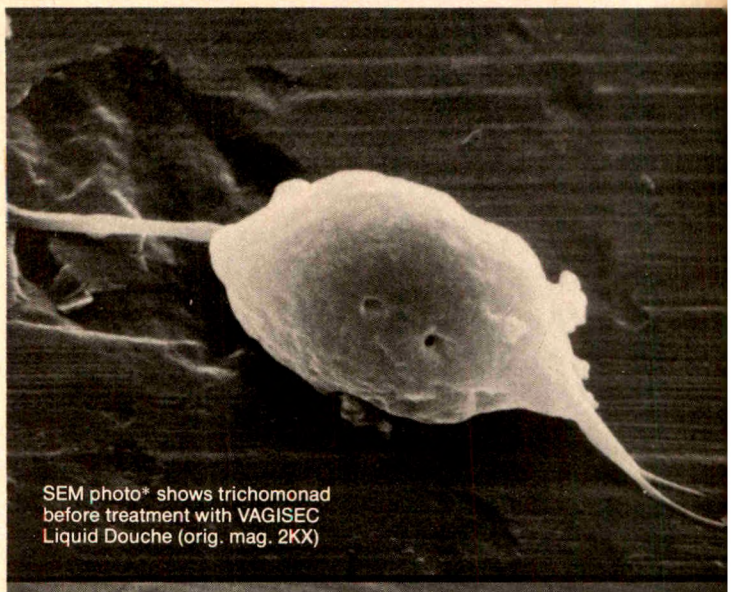
VAGISEC Douche/ VAGISEC PLUS Suppositories

regimen for the treatment of trichomoniasis... or mixed vaginal infections

VAGISEC Douche acts on the trichomonads directly—far faster than most systemic medication. It penetrates the vaginal creases and folds; cleanses and dissolves mucinous material; and prevents buildup of microorganisms. Relief from itching, burning, leukorrhea and malodor is almost immediate.

VAGISEC PLUS Suppositories combines the same proved trichomonacide with effective antibacterial action against susceptible strains of staph, strep and coliform organisms,[3] and is particularly useful in mixed infections.

The combination douche/suppositories regimen is recommended in all cases, except during pregnancy, when douching is not recommended. Strict adherence to the treatment program is essential for therapeutic success.



SEM photo* shows trichomonad before treatment with VAGISEC Liquid Douche (orig. mag. 2KX)



15 seconds after treatment, photo shows cell wall destruction and loss of flagella (orig. mag. 5KX)

VAGISEC Liquid Douche/VAGISEC PLUS Suppositories
Contraindications: Douching is not recommended during pregnancy. VAGISEC Liquid Douche and VAGISEC PLUS Suppositories are spermicidal and should not be used on days when the patient is trying to conceive. **Precautions:** *Therapeutic Treatment:* Recurrence of vaginitis often indicates extravaginal foci or infection in cervical, vestibular and urethral glands, etc., or reinfection by the sexual partner. During treatment, patient should refrain from intercourse or the partner should wear a prophylactic. To prevent flare-ups after completion of therapy and for continued vaginal cleanliness, the patient is advised to continue with VAGISEC Liquid as a regular douche, but no more than twice weekly unless otherwise directed by physician. **Side Effects:** No significant side effects reported to date. Any minor irritation is alleviated by discontinuance of douche for a single day. **Administration and Dosage:** *Office Treatment (Adult):* For the treatment of vaginal trichomoniasis and mixed vaginal infections, best results are obtained by scrubbing the vagina with VAGISEC Liquid, diluted 1:100, by the physician in the office; 3 scrubs the first week, 2 the second. A suppository is inserted after each office scrub in the Liquid/Suppository regimen. Patient should be instructed to continue treatment at home. *Home Treatment:* Liquid/Suppository regimen: In all instances, the combination douche and suppositories are recommended for home use. The usual home treatment is VAGISEC Liquid Douche in the morning, followed by a VAGISEC PLUS Suppository inserted deep in the vagina and a second suppository inserted in like manner at bedtime, daily, for a period of 14 days. For those physicians who feel it important to treat the patient through the complete menstrual cycle, the Liquid/Suppository regimen may be continued throughout the month. It is advisable to continue treatment through two menstrual periods. Treatment should be omitted the night and morning preceding an office visit. Patients should be reexamined 3 days after home treatment has been discontinued. The full course of therapy must be completed to eliminate the infecting microorganisms from the vagina. In chronic or stubborn cases, therapy may be repeated with no interval between courses. During treatment, patient should refrain from intercourse, or the partner should wear a prophylactic. No patient should be considered cured until vaginal smears or cultures, taken at monthly intervals for 3 months following treatment, show absence of trichomonads and a return to the normal vaginal flora. **How Supplied:** VAGISEC Liquid—4 oz. plastic bottle. VAGISEC PLUS Suppositories—box of 28 3-gram suppositories, foil-wrapped, with inserter. *Federal law prohibits dispensing VAGISEC PLUS suppositories without prescription. More detailed professional information available on request.*

*SEM photographs from S.T.E.M. Laboratories, Inc., Kansas City, Missouri 64127

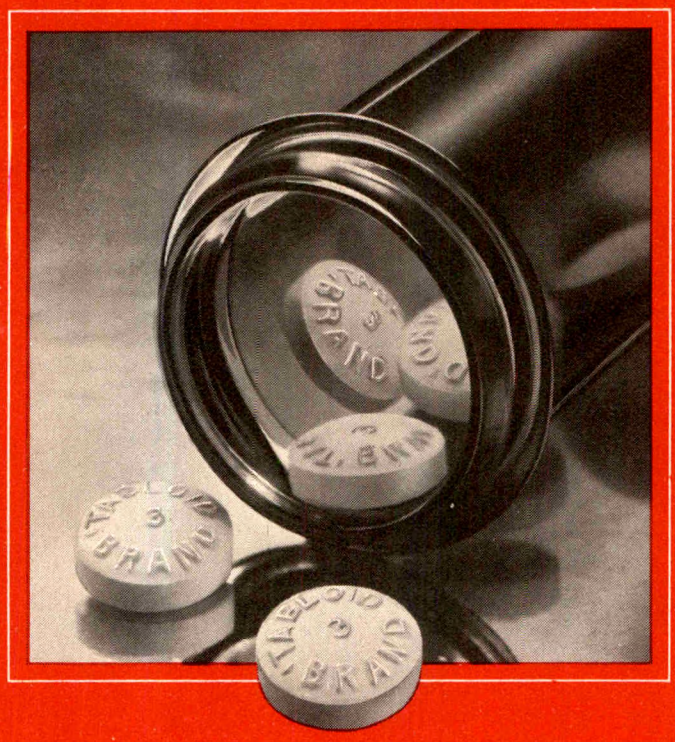
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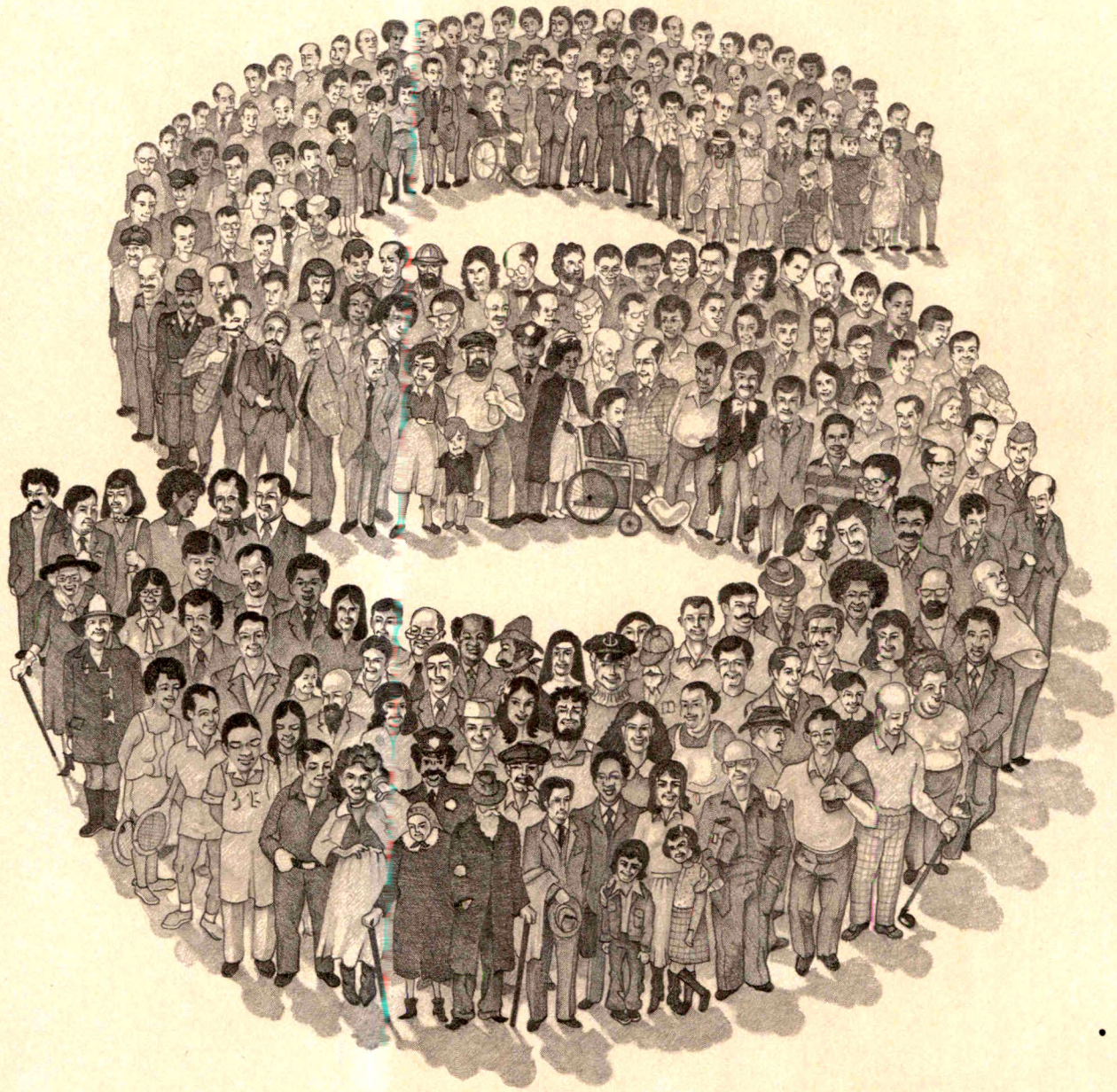
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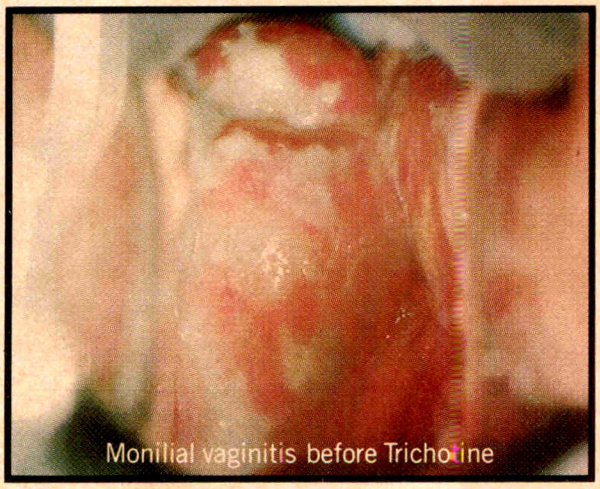
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James Henry Bennet
London, John Churchill, 1845

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You're looking at the only medical reason to recommend a douche.



Monilial vaginitis before Trichotine



Monilial vaginitis after Trichotine

When douching can enhance therapy of vaginitis, as in the photographs above, it has a definite place in medicine. And such evidence, as described by numerous clinical investigators over the years, is exactly the reason Trichotine® receives extensive professional recommendation.

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Cleanses better than acid douches/Works differently than iodophor douches.

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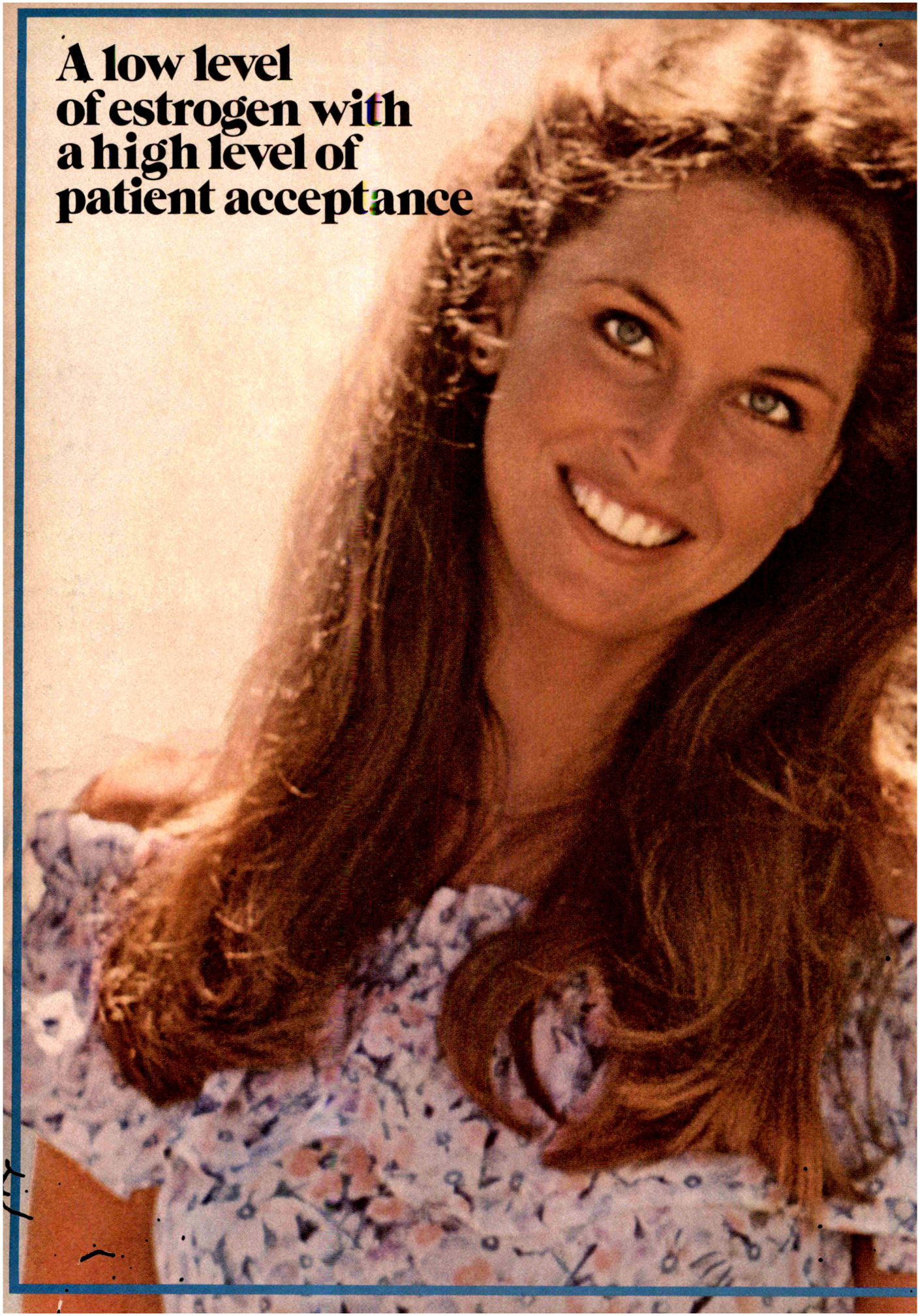
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Mishell, D.: Current Status of Oral Contraceptive Steroids, Clin. Obstet. Gynecol. *19*:743-764 (December) 1976.

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Contraindications—Thrombophlebitis, thromboembolic disorders, cerebral vascular disease, myocardial infarction or coronary artery disease, or past history of these; known or suspected breast carcinoma, estrogen-dependent neoplasia, or pregnancy; undiagnosed abnormal vaginal bleeding; markedly impaired liver function; past or present, benign or malignant liver tumors.

Warnings

Cigarette-smoking increases risk of serious cardiovascular side effects from OC use. Risk increases with age and heavy smoking (15 or more cigarettes/day) and is quite marked in women over 35. OC users should be strongly advised not to smoke.

OCs are associated with increased risk of several serious conditions including venous and arterial thromboembolism, thrombotic and hemorrhagic stroke, myocardial infarction, visual disorders, hepatic tumors, gallbladder disease, hypertension, fetal abnormalities. Practitioners should be familiar with the available information relating to these and other risks.

1. Thromboembolic disorders and other vascular problems—Increased risk of thromboembolic and thrombotic disease associated with OCs is well established. A British study showed increased relative risk for fatal venous thromboembolism, 2 British and 3 U.S. studies increased relative risk for nonfatal venous thromboembolism. Two U.S. studies showed increased relative risk for stroke, not shown in prior British studies. It was estimated OC users were 2–11 times more likely than nonusers to manifest these diseases without evident cause. In a British study of idiopathic deep vein thrombosis and pulmonary embolism, projected hospitalization rates for ages 16-40 were 47/year/100,000 users and 5 for nonusers. In a British mortality study, overall excess mortality from pulmonary embolism or stroke was 1.3–3.4 deaths/year/100,000 users and increased with age. Cerebrovascular Disorders—In a U.S. study of stroke with and without predisposing causes, risk of hemorrhagic stroke was estimated as 2 times greater and thrombotic stroke 4.0–9.5 times greater in users. Mortality trends in 21 countries indicate that, since OC introduction, changes in mortality from nonrheumatic cardiovascular disease were associated with changes in the prevalence of OC use. The Royal College of GPs reported on its prospective study comparing users and nonusers: "A statistically significant higher rate of reporting of cerebrovascular accidents in Takers is evident, but the numbers are too small to justify an estimation of the degree of risk." They reported more superficial and deep vein thrombosis in users. A 1977 analysis showed a 5-fold increased mortality in users from circulatory diseases, mainly myocardial infarction (MI) and hemorrhagic stroke. Excess mortality was associated with age, smoking and duration of use. In 1976 a British Family Planning Association study found a highly significant association between OC use and stroke though total numbers were small; the increased risk for venous thrombosis and pulmonary embolism was about 4-fold and statistically highly significant. Circulatory disease mortality was significantly greater in users. Myocardial Infarction—An increased risk of MI associated with OC use was reported in Britain, as previously suspected. The morbidity study found the greater the number of risk factors for coronary artery disease (smoking, hypertension, hypercholesterolemia, obesity, diabetes, history of pre-eclamptic toxemia) the higher the MI risk, regardless of OC use. OCs were considered an additional risk factor. The excess rate of fatal MI in Britain was about 3.5/year/100,000 users aged 30–39 and 20 for ages 40–44. (These are based on British vital statistics with acute MI death rates 2–3 times less than the U.S. Similar estimates for U.S. are 25.7 for users aged 30–39 with predispositions vs. 1.5 without; for ages 40–44, 86.2 vs. 5.1.) Excess hospitalization rate for nonfatal MI in Britain was about 3.5/year/100,000 users aged 30–39 and 47 for ages 40–44. Smoking is a major predisposing condition to MI. In terms of relative risk, nonsmoking OC users are twice as likely to have fatal MI as nonsmoking nonusers. Smoking users have a 5-fold greater risk of fatal MI as nonsmoking users, but a 10–12-fold greater risk than nonsmoking nonusers. Amount of smoking is an important factor. In determining importance of these risks, give serious consideration to rates in table below. Importance of other predispositions cited above in determining relative and absolute risks has not been quantified; it is likely the same synergism exists, but perhaps to a lesser extent.

Estimated Mortality Rate from Myocardial Infarction per 100,000 Women/Year

	Aged 30–39		Aged 40–44	
	Users	Nonusers	Users	Nonusers
All smokers	10.2	2.6	62.0	15.9
≥15 cigarettes daily	13.0	5.1	78.7	31.3
<15 cigarettes daily	4.7	0.9	28.6	5.7
Nonsmokers	1.8	1.2	10.7	7.4
Smokers and nonsmokers	5.4	1.9	32.8	11.7

Risk of Dose—Reports of thromboembolism after use of OCs with ≥50 mcg. estrogen received by drug safety committees in Britain, Sweden and Denmark were compared with the distribution expected from market research sales estimates. A positive correlation was found between estrogen dose and reporting of thromboembolism, including coronary thrombosis, in excess of that predicted by sales. OCs with ≥100 mcg. estrogen were associated with higher thromboembolism risk than those with 50–80 mcg. The authors suggested that estrogen quantity may not be the sole factor. Any influence of progestogens was not considered, which may be responsible for certain discrepancies in the data. No significant differences were noted between OCs containing the same estrogen dose nor between ethinyl estradiol and mestranol. Studies on thromboembolic risk with progestogen-only OCs have not been done. Cases have been reported for these OCs and they are not presumed free of excess risk. In a U.S. case-controlled study, relative risk of OC use 1 month before hospitalization for various types of thromboembolism was calculated. If relative estrogenic potency and possible influence of different progestogens are ignored, OCs may be divided into those with <100 mcg. and those with ≥100 mcg. estrogen. For all cases combined, larger doses were associated with only slightly higher relative risk; for idiopathic cases relative risk was doubled with larger doses, but confidence limits overlapped and differences were not significant. Apparently there was no increased risk for cases with predispositions. Thromboembolic risk in users and nonusers increases with age. OCs have been considered an independent risk factor. Excess Mortality from Circulatory Diseases—A U.K. prospective study estimated annual mortality from circulatory diseases for OC users and nonusers according to age, smoking habits and duration of use. Excess mortality was 20/100,000 users (5 for ages 15–34, 33 for ages 35–44, 140 for ages 45–49), the risk being concentrated in older women, long-term users, and smokers. Interrelationships of age, smoking and duration of use could not be examined, nor could effects of continuous vs. intermittent use. Though circulatory mortality was increased 10-fold in users of >5 years, all deaths were in women over age 34. Until more under-35 users of 5+ continuous years are available, size of relative risk for this age group cannot be given. Risk of circulatory disease may have persisted after discontinuance of OCs. One study estimated risk of death with various contraceptive methods, each estimate including risk of method (e.g., thromboembolism for OCs) plus risk due to pregnancy or abortion in cases of method failure. This latter risk varies with effectiveness. It concluded mortality with all methods is low and below that of childbirth, except for OC users over 40 who smoke. Heavy smokers have double the risk of smokers as a class, light smokers about half. Mortality associated with OC use in nonsmokers over 40 is higher than with any other method in that age group. Lowest mortality is with the condom or diaphragm backed up by early legal abortion. Risk of thromboembolic and thrombotic disease associated with OCs increases with age after 30 and, for MI, is further increased by hypertension, hypercholesterolemia, obesity, diabetes, history of pre-eclamptic toxemia, and especially cigarette smoking. Based on current data, the chart gives gross estimates of risk of death from circulatory disorders associated with OCs:

Risk is: A—very high, B—high, C—moderate, D—low.	Age: <30	30–39	≥40
Heavy smokers (≥15/day)	C	B	A
Light smokers (<15/day)	D	C	B
Nonsmokers, no predispositions	D	C,D	C
Nonsmokers, with predispositions	C	C,B	B,A

Physician and patient should be alert to earliest manifestations of thromboembolic and thrombotic disorders (e.g., thrombophlebitis, pulmonary embolism, cerebrovascular insufficiency, coronary artery disease, myocardial infarction, retinal thrombosis, mesenteric thrombosis). Should any of these occur or be suspected, discontinue OCs immediately. A 4–7-fold increased risk of postsurgery thromboembolism was reported in users; if feasible discontinue OCs at least 4 weeks before elective surgery or during prolonged immobilization and do not resume until at least 4 weeks postsurgery. Thromboembolic risk may be increased for users with blood types A, B or AB. **2.** Ocular lesions—Neuro-ocular lesions, such as optic neuritis or retinal thrombosis have been associated with OCs. Discontinue if there is unexplained, gradual or sudden, partial or complete loss of vision; proptosis or diplopia; papilledema; or evidence of retinal vascular lesions. Institute diagnostic and therapeutic measures. **3.** Carcinoma—Long-term estrogen in certain animals increases carcinomas such as those of breast, uterus, cervix, vagina, ovary, liver, pituitary. Some synthetic progestogens, none currently in OCs, increase incidence of benign and malignant mammary nodules in dogs. There is now evidence that estrogens increase risk of human endometrial carcinoma. In several case-controlled studies increased relative risk (3.1–13.9 times) associated endometrial carcinoma with prolonged estrogen for menopausal symptoms. Risk was independent of other known risk factors and depended on duration of use and dose. This is supported by increased endometrial cancer incidence since 1969 in 8 U.S. areas with cancer-reporting systems, which may be related to rapidly expanding estrogen use. There is no evidence that natural estrogens are more or less hazardous than synthetics at equi-estrogenic doses. Of the first 30 cases of endometrial carcinoma in OC users under 40, those without predispositions (e.g., irregular bleeding before OCs, polycystic ovaries) occurred nearly always with no-longer-marketed sequential OCs. No statistical association is reported suggesting increased endometrial cancer with combination or progestogen-only OCs, though individual cases have been reported. Studies show no increased breast cancer with OCs or estrogens. However, greater risk was noted in OC users with benign breast disease or long-term (2–4 years) use. Risk of breast cancer with menopausal estrogens rose and further increased with duration of follow-up. Decreased benign breast tumors in OC users is well known. Some studies suggested increased risk of cervical dysplasia, erosion and carcinoma in long-term users; cause and effect is not established. Cervical microglandular hyperplasia has been reported. In summary, there is no confirmed evidence from human studies of increased cancer risk with OCs. Close surveillance is, however, essential. In undiagnosed persistent or recurrent abnormal vaginal bleeding, consider nonfunctional causes and take appropriate diagnostic measures to rule out malignancy. Carefully monitor users with a strong family history of breast cancer or with breast nodules, fibrocystic disease, recurrent cystic mastitis, abnormal mammograms, or cervical dysplasia. **4.** Hepatic adenomas, hepatomas, hamartomas, regenerating nodules, focal nodular hyperplasia, hemangiomas, hepatocellular carcinoma, etc. have been associated with OCs. In 1 study OC formulations with high "hormonal potency" were associated with higher risk. Though benign these hepatic lesions may rupture and cause fatal hemoperitoneum in short- or long-term users. Two studies related risk to duration of use, being much greater after ≥4 years. Consider such lesions in users with abdominal pain, tenderness, mass or shock. About 25% present with abdominal masses; up to half with acute hemoperitoneum. Routine radiologic and lab studies may not be helpful; liver scans may show a focal defect. Hepatic arteriography or CAT may be useful in diagnosis. Hepatocellular carcinoma was noted in a few users. OCs are contraindicated in case of past or present, benign or malignant liver tumors. **5.** Use in or immediately preceding pregnancy, birth defects, malignancy in offspring—Estrogens or progestogens during early pregnancy may seriously damage offspring. Females exposed in utero to DES and other nonsteroidal estrogens may have increased risk of vaginal or cervical cancer. Though OCs may not enhance this risk, monitor such patients carefully. From 30–90% of DES-exposed women develop benign vaginal or cervical adenosis, which could be premalignant. Males so exposed may develop urogenital defects. Other estrogens may mimic DES. Reports relate fetal exposure to female sex hormones and congenital anomalies, e.g., multiple anomalies described by VACTERL for vertebral, anal, cardiac, tracheoesophageal, renal and limb defects. There appears preferential expression by males. There was a 4.7-fold increased risk of limb-reduction defects in infants exposed in utero to sex hormones (OCs, hormonal withdrawal pregnancy tests or treatment for threatened abortion). Some exposures were very short, being only a few days. Cardiovascular defects in children exposed to female hormones, including OCs, during early pregnancy occurred at 18.2/1000 births, compared to 7.8 for those unexposed ($P < .05$). Female sex hormones were used for threatened or habitual abortion, but there is considerable evidence estrogens are ineffective and no evidence progestogens are effective. Triploidy and possibly other polyploidy may be increased in abortuses from women becoming pregnant soon post-OC. These almost always abort spontaneously. It is unknown if spontaneous abortion is increased soon after stopping OCs. Safety of OCs in pregnancy has not been demonstrated. Rule out pregnancy in using OCs and always consider it if withdrawal bleeding does not occur. If 2 consecutive periods are missed rule out pregnancy before continuing. If user deviates from regimen, consider pregnancy at first missed period and withhold OCs. If pregnancy is confirmed, apprise patient of potential fetal risks and discuss continuation of pregnancy. Users discontinuing for pregnancy should use alternative contraception for 3 months before attempting to conceive, though this is not based on precise information. Do not use progestogen-only or progestogen-estrogen drugs as pregnancy tests. **6.** Gallbladder disease risk surgically confirmed, appeared after 2 years' use and doubled after 4–5 years in 1 study; it appeared in 6–12 months' use in another. **7.** Carbohydrate & lipid metabolism—Decreased glucose tolerance occurs in a significant number of users: carefully observe diabetic and prediabetic patients. Triglycerides and total phospholipids may increase. **8.** Elevated blood pressure (BP) occurs in some users in a few months, and degree may relate to progestogen dose. Hypertension prevalence in users is no higher than in nonusers in the first year, but increases with longer exposure; in the 5th year it is 2½–3 times the first year. Age is strongly correlated with hypertension in users. Those with history of elevated BP (hypertension), pre-existing renal disease, history of toxemia or elevated BP in pregnancy, familial tendency to hypertension or its consequences, or history of excessive weight gain or fluid retention during menstrual cycles may be more likely to develop elevated BP on OCs and thus should be monitored closely. Even though elevated BP may be in the "normal" range, do not ignore clinical implications. Follow closely, particularly those with other risk factors for cardiovascular disease or stroke. High BP may or may not persist after stopping OCs. **9.** Headache—Onset or exacerbation of migraine or development of headache of a new pattern that is recurrent, persistent or severe requires stopping OCs and evaluating cause. **10.** Bleeding irregularities—Breakthrough bleeding (BTB), spotting and amenorrhea are frequent reasons for discontinuing. In BTB, as in all cases of irregular bleeding, consider nonfunctional causes. In undiagnosed persistent or recurrent bleeding, rule out pregnancy or malignancy. If pathology is excluded, time or change to another product may suffice. Change to a higher estrogen OC only when necessary as this may increase thromboembolic risk. Those with a history of oligomenorrhea or secondary amenorrhea or without established regular cycles may be anovulatory or amenorrheic after discontinuing. Those with such problems should be so informed and other methods encouraged. Post-use anovulation, possibly prolonged, may occur in women without previous irregularities. Higher incidence of galactorrhea and of pituitary tumors (e.g., adenomas) has been associated with postpill amenorrhea. One study reported 16-fold increased prevalence of pituitary prolactin-secreting tumors in patients with postpill amenorrhea when galactorrhea was present. **11.** Ectopics—In failures with combination OCs, the ratio of ectopic to intrauterine pregnancies is no higher than in nonusers. There may be an increased risk of ectopics after discontinuing. **12.** Breast feeding—OCs may decrease quantity and quality of milk. A small fraction of OC steroids appears in milk. Effects if any on the child are unknown. If feasible defer OCs until after weaning. **13.** Infertility may occur in women discontinuing OCs, which appears independent of duration of use. While impairment diminishes with time, there is still an appreciable difference in nulliparous but not parous women after 30 months; difference is negligible after 42 months.

Precautions—Conduct complete history and physical prior to OC use and annually thereafter. Include breasts, abdomen and pelvis, with BP, pap and lab tests. Pre-existing uterine leiomyomata may enlarge. Mental depression may occur; with positive history, observe carefully and discontinue if serious recurrence. Fluid retention may occur; prescribe cautiously and monitor carefully in convulsive disorders, migraine, asthma, or cardiac, hepatic or renal dysfunction. History of jaundice in pregnancy increases risk of recurrence on OCs; observe carefully and discontinue if jaundice occurs. Steroids may be poorly metabolized in liver dysfunction and should be given cautiously. Tryptophan metabolism may be disturbed and result in pyridoxine deficiency; megaloblastic anemia has been reported. Serum folate may be depressed and may be exacerbated in post-OC pregnancy. Advise pathologist of OC use when submitting specimens. Endocrine and liver function tests may be altered; repeat abnormal tests after stopping for 2 months. These have been observed: increased BSP retention and other abnormalities in liver function tests; increased prothrombin and coagulation factors VII, VIII, IX, X; decreased antithrombin III, increased platelet aggregability; increased thyroid-binding globulin leading to increased circulating total thyroid hormone (PBI, T^4); decreased T^3 uptake, unaltered free T^4; decreased pregnanediol excretion; reduced metyrapone response; increased blood transcortin, corticosteroid, triglyceride, phospholipid; reduced serum folate; impaired glucose tolerance; altered plasma trace minerals. Influence of prolonged OC use on pituitary, ovarian, adrenal, hepatic, or uterine function, or on immune response is not established. OCs may mask onset of climacteric. Information for patients—see patient labeling. Drug interactions—OC effectiveness may be decreased and more BTB occur with rifampicin, isoniazid, ampicillin, neomycin, penicillin V, chloramphenicol, sulfonamides, nitrofurantoin, barbiturates, phenytoin, primidone, phenylbutazone, analgesics, tranquilizers, antimigraines. OCs may alter effectiveness of drugs such as oral anticoagulants, anticonvulsants, tricyclic antidepressants, antihypertensives, vitamins, hypoglycemics.

Adverse Reactions—Increased risk of the following serious adverse reactions has been associated with OCs: thrombophlebitis and thrombosis; pulmonary embolism; myocardial infarction and coronary thrombosis; cerebral thrombosis; cerebral hemorrhage; hypertension; gallbladder disease; benign adenomas and other hepatic lesions, with or without intra-abdominal bleeding; congenital abnormalities. There is evidence of association between the following conditions and OCs, though confirmatory studies have not been done: mesenteric thrombosis; Budd-Chiari syndrome, neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis. The following have been reported with OCs and are believed drug related: nausea, vomiting, gastrointestinal symptoms, breakthrough bleeding, spotting, change in menstrual flow, dysmenorrhea, amenorrhea during and after use, infertility post-OC, edema, chloasma or melasma, which may persist post-OC, breast changes (tenderness, enlargement, secretion), weight changes, change in cervical erosion and secretion, endocervical hyperplasia, lactation decrease, cholestatic jaundice, migraine, enlarged uterine leiomyomata, allergic rash, mental depression, reduced carbohydrate tolerance, vaginal candidiasis, change in corneal curvature (steepening), intolerance to contact lenses. The following have been reported and association has not been confirmed or refuted: premenstrual-like syndrome, cataracts, libido changes, chorea, appetite changes, cystitis-like syndrome, headache, paresthesia, nervousness, dizziness, auditory disturbances, rhinitis, fatigue, backache, hirsutism, scalp hair loss, erythema multiforme or nodosum, hemorrhagic eruption, itching, vaginitis, porphyria, impaired renal function, anemia, pancreatitis, hepatitis, colitis, gingivitis, lupus erythematosus, rheumatoid arthritis, pituitary tumors (e.g., adenoma) with amenorrhea and/or galactorrhea after use, endometrial, cervical and breast carcinoma.

Acute overdosage—Serious ill effects have not been reported after large acute doses of OCs in young children, but nausea and withdrawal bleeding might occur.

Important note—Full prescribing information should be consulted prior to use and is available on request.

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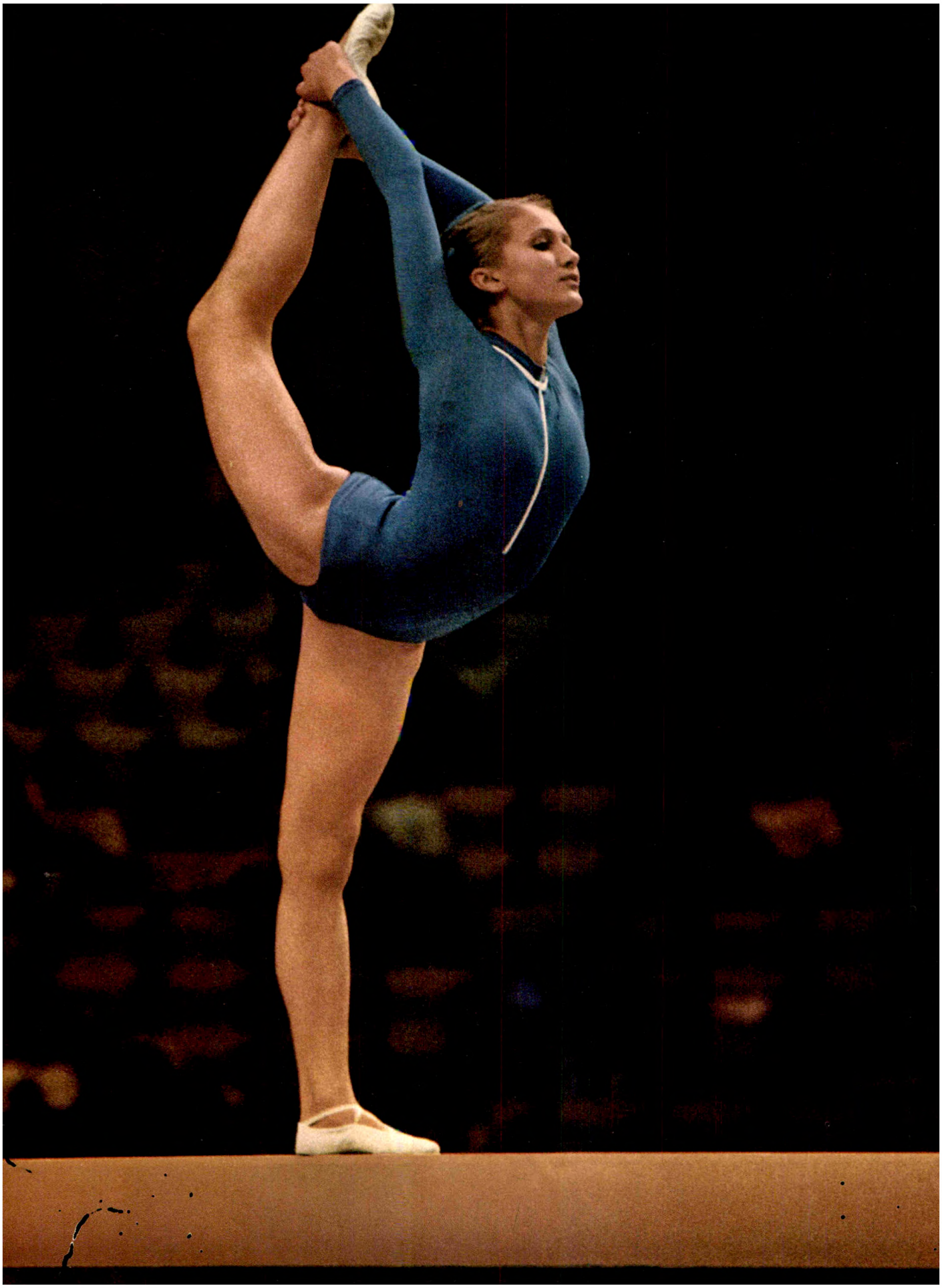
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ModiCon combines a low dose of estrogen (0.035 mg ethinyl estradiol) with a low dose of progestin (0.5 mg norethindrone). In clinical trials, the pregnancy rate in **1,168** patients completing **16,345** cycles was only **0.22** per 100 woman-years.

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ModiCon

†Serious as well as minor side effects have been reported with the use of oral contraceptives. These include thromboembolic disease. The physician should remain alert to the earliest manifestations of any symptoms of serious disease and discontinue oral contraceptive therapy when appropriate. The physician should be fully aware of the complete Prescribing Information for this product.

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Raritan, New Jersey 08869

OJ 882R1

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IMPORTANT NOTE—This information is a BRIEF SUMMARY of the complete prescribing information provided with the product and therefore should not be used as the basis for prescribing the product. This summary was prepared by deleting from the complete prescribing information certain text, tables, and references. The physician should be thoroughly familiar with the complete prescribing information and patient information before prescribing the product.

INDICATION: CONTRACEPTION. The pregnancy rate in women using conventional combination oral contraceptives (containing 35 mcg or more of ethinyl estradiol or 50 mcg or more of mestranol) is generally reported as less than one pregnancy per 100 woman-years of use. Slightly higher rates (somewhat more than one pregnancy per 100 woman-years of use) are reported for some combination products containing 35 mcg or less of ethinyl estradiol, and rates on the order of three pregnancies per 100 woman-years are reported for the progestogen-only oral contraceptives. Table 1 gives ranges of pregnancy rates reported in the literature for other means of contraception. The efficacy of these means of contraception (except the IUD) depends upon the degree of adherence to the method.

Table 1: Pregnancies Per 100 Women-Years. IUD, less than 1-6; Diaphragm with spermicidal product (creams or jellies), 2-20; Condom, 3-36; Aerosol foams, 2-29; Jellies and creams, 4-36; Periodic abstinence (rhythm) all types, less than 1-47; 1. Calendar method, 14-47; 2. Temperature method, 1-20; 3. Temperature method—intercourse only in postovulatory phase, less than 1-7; 4. Mucus method, 1-25; No contraception, 60-80. **DOSE-RELATED RISK OF THROMBOEMBOLISM FROM ORAL CONTRACEPTIVES:** Two studies have shown a positive association between the dose of estrogens in oral contraceptives and the risk of thromboembolism. For this reason, it is prudent and in keeping with good principles of therapeutics to minimize exposure to estrogen. The oral contraceptive product prescribed for any given patient should be that product which contains the least amount of estrogen that is compatible with an acceptable pregnancy rate and patient acceptance. It is recommended that new acceptors of oral contraceptives be started on preparations containing .05 mg or less of estrogen.

CONTRAINDICATIONS: Oral contraceptives should not be used in women with any of the following conditions: 1. Thrombophlebitis or thromboembolic disorders. 2. A past history of deep vein thrombophlebitis or thromboembolic disorders. 3. Cerebral vascular or coronary artery disease. 4. Known or suspected carcinoma of the breast. 5. Known or suspected estrogen-dependent neoplasia. 6. Undiagnosed, abnormal genital bleeding. 7. Known or suspected pregnancy (see WARNINGS, No. 5).

WARNINGS

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

The use of oral contraceptives is associated with increased risk of several serious conditions including thromboembolism, stroke, myocardial infarction, hepatic adenoma, gallbladder disease, hypertension. Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks.

1. THROMBOEMBOLIC DISORDERS AND OTHER VASCULAR PROBLEMS. An increased risk of thromboembolic and thrombotic disease associated with the use of oral contraceptives is well established. Four principal studies in Great Britain and three in the United States have demonstrated an increased risk of fatal and nonfatal venous thromboembolism and stroke, both hemorrhagic and thrombotic. These studies estimate that users of oral contraceptives are 4 to 11 times more likely than nonusers to develop these diseases without evident cause. Overall excess mortality due to pulmonary embolism or stroke is on the order of 1.0 to 3.5 deaths annually per 100,000 users and increases with age. **CEREBROVASCULAR DISORDERS:** In a collaborative American study of cerebrovascular disorders in women with and without predisposing causes, it was estimated that the risk of hemorrhagic stroke was 2.0 times greater in users than in nonusers and the risk of thrombotic stroke was 4.0 to 9.5 times greater in users than in nonusers.

MYOCARDIAL INFARCTION: An increased risk of myocardial infarction associated with the use of oral contraceptives has been reported confirming a previously suspected association. These studies, conducted in the United Kingdom, found, as expected, that the greater the number of underlying risk factors for coronary artery disease (cigarette smoking, hypertension, hypercholesterolemia, obesity, diabetes, history of preeclamptic toxemia), the higher the risk of developing myocardial infarction, regardless of whether the patient was an oral contraceptive user or not. Oral contraceptives, however, were found to be a clear additional risk factor. The annual excess case rate (increased risk) of myocardial infarction (fatal and nonfatal) in oral contraceptive users was estimated to be approximately 7 cases per 100,000 women users in the 30-39 age group and 67 cases per 100,000 women users in the 40-44 age group. In terms of relative risk, it has been estimated that oral contraceptive users who do not smoke (smoking is considered a major predisposing condition to myocardial infarction) are about twice as likely to have a fatal myocardial infarction as nonusers who do not smoke. Oral contraceptive users who are also smokers have about a 5-fold increased risk of fatal infarction compared to users who do not smoke, but about a 10-to 12-fold increased risk compared to nonusers who do not smoke. Furthermore, the amount of smoking is also an important factor. In determining the importance of these relative risks, however, the baseline rates for various age groups must be given serious consideration. The importance of other predisposing conditions mentioned above in determining relative and absolute risks has not as yet been quantified; it is quite likely that the same synergistic action exists, but perhaps to a lesser extent. **Risk of Dose:** In an analysis of data derived from several national adverse reaction reporting systems, British investigators concluded that the risk of thromboembolism including coronary thrombosis is directly related to the dose of estrogen used in oral contraceptives. Preparations containing 100 mcg or more of estrogen were associated with a higher risk of thromboembolism than those containing 50-80 mcg of estrogen. Their analysis did suggest, however, that the quantity of estrogen may not be the sole factor involved. This finding has been confirmed in the United States. Careful epidemiological studies to determine the degree of thromboembolic risk associated with progestogen-only oral contraceptives have not been performed. Cases of thromboembolic disease have been reported in women using these products, and they should not be presumed to be free of excess risk. The risk of thromboembolic and thrombotic disorders, in both users and nonusers of oral contraceptives, increases with age. Oral contraceptives are, however, an independent risk factor for these events. **ESTIMATE OF EXCESS MORTALITY FROM CIRCULATORY DISEASES:** A large prospective study carried out in the United Kingdom estimated the mortality rate per 100,000 women per year from diseases of the circulatory system for users and nonusers of oral contraceptives according to age, smoking habits, and duration of use. The overall excess death rate annually from circulatory diseases for oral contraceptive users was estimated to be 20 per 100,000 (ages 15-34—5/100,000; ages 35-44—33/100,000; ages 45-49—140/100,000); the risk being concentrated in older women, in those with a long duration of use, and in cigarette smokers. It was not possible, however, to examine the interrelationships of age, smoking, and duration of use, nor to compare the effects of continuous versus intermittent use. Although the study showed a 10-fold increase in death due to circulatory diseases in users for five or more years, all of these deaths occurred in women 35 or older. Until larger numbers of women under 35 with continuous use for five or more years are available, it is not possible to assess the magnitude of the relative risk for this younger age group. This study reports that the increased risk of circulatory diseases may persist after the pill is discontinued. Another study published at the same time confirms a previously reported increase of mortality in pill users from cardiovascular disease. The available data from a variety of sources have been analyzed to estimate the risk of death associated with various methods of contraception. The estimates of risk of death for each method include the combined risk of the contraceptive method (e.g., thromboembolic and thrombotic disease in the case of oral contraceptives) plus the risk attributable to pregnancy or abortion in the event of method failure. This latter risk varies with the effectiveness of the contraceptive method. The findings of this analysis are shown in Figure 1 below. The study concluded that the mortality associated with all methods of birth control is low and below that associated with childbirth, with the exception of oral contraceptives in women over 40 who smoke. (The rates given for pill only/smokers for each age group are for smokers as a class. For "heavy" smokers [more than 15 cigarettes a day], the rates given would be about double; for "light" smokers [less than 15 cigarettes a day], about 50 percent.) The mortality associated with oral contraceptive use in nonsmokers over 40 is higher than with any other method of contraception in that age group. The lowest mortality is associated with the condom or diaphragm backed up by early abortion. The risk of thromboembolic and thrombotic disease associated with oral contraceptives increases with age after approximately age 30 and, for myocardial infarction, is further increased by hypertension, hypercholesterolemia, obesity, diabetes, or history of preeclamptic toxemia and especially by cigarette smoking. The risk of myocardial infarction in oral contraceptive users is substantially increased in women age 40 and over, especially those with other risk factors. Based on the data currently available, the following chart gives a gross estimate of the risk of death from circulatory disorders associated with the use of oral contraceptives:

SMOKING HABITS AND OTHER PREDISPOSING CONDITIONS—RISK ASSOCIATED WITH USE OF ORAL CONTRACEPTIVES

Age	Below 30	30-39	40+	
Heavy smokers	C	B	A	A—Use associated with very high risk.
Light smokers	D	C	B	B—Use associated with high risk.
Nonsmokers (no predisposing conditions)	D	C,D	C	C—Use associated with moderate risk.
Nonsmokers (other predisposing conditions)	C	C,B	B,A	D—Use associated with low risk.

The physician and the patient should be alert to the earliest manifestations of thromboembolic and thrombotic disorders (e.g., thrombophlebitis, pulmonary embolism, cerebrovascular insufficiency, coronary occlusion, retinal thrombosis, and mesenteric thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately. A four- to six-fold increased risk of postsurgery thromboembolic complications has been reported in oral contraceptive users. If feasible, oral contraceptives should be discontinued at least four weeks before surgery of a type associated with an increased risk of thromboembolism or prolonged immobilization. 2. OCULAR LESIONS. There have been reports of neuro-ocular lesions such as optic neuritis or retinal thrombosis associated with the use of oral contraceptives. Discontinue oral contraceptive medication if there is unexplained, sudden or gradual, partial or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal vascular lesions and institute appropriate diagnostic and therapeutic measures. 3. CARCINOMA. Long-term continuous administration of either natural or synthetic estrogen in certain animal species increases the frequency of carcinoma of the breast, cervix, vagina, and liver. Certain synthetic progestogens, none currently contained in oral contraceptives, have been noted to increase the incidence of mammary nodules, benign and malignant, in dogs. In humans, three case control studies have reported an increased risk of endometrial carcinoma associated with the prolonged use of exogenous estrogen in postmenopausal women. One publication reported on the first 21 cases submitted by physicians to a registry of cases of adenocarcinoma of the endometrium in women under 40 on oral contraceptives. Of the cases found in women without predisposing risk factors for adenocarcinoma of the endometrium (e.g., irregular bleeding at the time oral contraceptives were first given, polycystic ovaries), nearly all occurred in women who had used a sequential oral contraceptive. These products are no longer marketed. No evidence has been reported suggesting an increased risk of endometrial cancer in users of conventional combination or progestogen-only oral contraceptives. Several studies have found no increases in breast cancer in women taking oral contraceptives or estrogens. One study, however, while also noting no overall increased risk of breast cancer in women treated with oral contraceptives, found an excess risk in the subgroups of oral contraceptive users with documented benign breast disease. A reduced occurrence of benign breast tumors in users of oral contraceptives has been well-documented. In summary, there is at present no confirmed evidence from human studies of an increased risk of cancer associated with oral contraceptives. Close clinical surveillance of all women taking oral contraceptives is, nevertheless, essential. In all cases of undiagnosed persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be taken to rule out malignancy. Women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease or abnormal mammograms should be monitored with particular care if they elect to use oral contraceptives instead of other methods of contraception.

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women, by regimen of control and age of woman.

	15-19	20-24	25-29	30-34	35-39	40-44
No method	5.5	5.2	7.1	14.0	19.3	21.9
Abortion only	2.3	2.5	2.5	5.2	9.8	6.6
Pill only-nonsmokers	1.3	1.4	1.4	2.2	4.5	3.1
Pill only-smokers	1.5	1.6	1.6	10.8	13.4	58.9
IUDs only	1.1	1.2	1.2	1.4	1.6	1.4
Traditional contraception only	1.1	1.4	1.9	3.7	4.7	4.0
Traditional contraception and abortion	0.3	0.4	0.4	0.8	1.4	0.8

4. HEPATIC TUMORS. Benign hepatic adenomas have been found to be associated with the use of oral contraceptives. One study showed that oral contraceptive formulations with high hormonal potency were associated with a higher risk than lower potency formulations. Although benign, hepatic adenomas may rupture and may cause death through intra-abdominal hemorrhage. This has been reported in short-term as well as long-term users of oral contraceptives. Two studies relate risk with duration of use of the contraceptive, the risk being much greater after four or more years of oral contraceptive use. While hepatic adenoma is a rare lesion, it should be considered in women presenting abdominal pain and tenderness, abdominal mass or shock. A few cases of hepatocellular carcinoma have been reported in women taking oral contraceptives. The relationship of these drugs to this type of malignancy is not known at this time. 5. USE IN OR IMMEDIATELY PRECEDING PREGNANCY, BIRTH DEFECTS IN OFFSPRING, AND MALIGNANCY IN FEMALE OFFSPRING. The use of female sex hormones—both estrogenic and progestational agents—during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a nonsteroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare. This risk has been estimated to be on the order of 1 to 4 in 1000 exposures. Although there is no evidence at the present time that oral contraceptives further enhance the risk of developing this type of malignancy, such patients should be monitored with particular care if they elect to use oral contraceptives instead of other methods of contraception. Furthermore, a high percentage of such exposed women (from 30 to 90%) have been found to have epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether this condition is a precursor of vaginal malignancy. Male children so exposed may develop abnormalities of the urogenital tract. Although similar data are not available with the use of other estrogens, it cannot be presumed that they would not induce similar changes. An increased risk of congenital anomalies, including heart defects and limb defects, has been reported with the use of sex hormones, including oral contraceptives, in pregnancy. One case control study has estimated a 4.7-fold increase in risk of limb-reduction defects in infants exposed in utero to sex hormones (oral contraceptives, hormonal withdrawal tests for pregnancy or attempted treatment for threatened abortion). Some of these exposures were very short and involved only a few days of treatment. The data suggest that the risk of limb-reduction defects in exposed fetuses is somewhat less than one in 1,000 live births. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well-controlled studies that progestogens are effective for these uses. There is some evidence that triploidy and possibly other types of polyploidy are increased among abortuses from women who become pregnant soon after ceasing oral contraceptives. Embryos with these anomalies are virtually always aborted spontaneously. Whether there is an overall increase in spontaneous abortion of pregnancies conceived soon after stopping oral contraceptives is unknown. It is recommended that for any patient who has missed two consecutive periods, pregnancy should be ruled out before continuing the contraceptive regimen. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at the time of the first missed period (or after 45 days from the last menstrual period if the progestogen-only oral contraceptives are used), and further use of oral contraceptives should be withheld until pregnancy has been ruled out. If pregnancy is confirmed, the patient should be apprised of the potential risks to the fetus and the advisability of continuation of the pregnancy should be discussed in the light of these risks. It is also recommended that women who discontinue oral contraceptives with the intent of becoming pregnant use an alternate form of contraception for a period of time before attempting to conceive. Many clinicians recommend three months although no precise information is available on which to base this recommendation. The administration of progestogen-only or progestogen-estrogen combinations to induce withdrawal bleeding should not be used as a test of pregnancy. 6. GALLBLADDER DISEASE. Studies report an increased risk of surgically confirmed gallbladder disease in users of oral contraceptives and estrogens. In one study, an increased risk appeared after two years of use and doubled after four or five years of use. In one of the other studies, an increased risk was apparent between six and twelve months of use. 7. CARBOHYDRATE AND LIPID METABOLIC EFFECTS. A decrease in glucose tolerance has been observed in a significant percentage of patients on oral contraceptives. For this reason, prediabetic and diabetic patients should be carefully observed while receiving oral contraceptives. An increase in triglycerides and total phospholipids has been observed in patients receiving oral contraceptives. The clinical significance of this finding remains to be defined. 8. ELEVATED BLOOD PRESSURE. An increase in blood pressure has been reported in patients receiving oral contraceptives. In some women hypertension may occur within a few months of beginning oral contraceptive use. In the first year of use, the prevalence of women with hypertension is low in users and may be no higher than that of a comparable group of nonusers. The prevalence in users increases, however, with longer exposure, and in the fifth year of use is two and a half to three times the reported prevalence in the first year. Age is also strongly correlated with the development of hypertension in oral contraceptive users. Women who previously have had hypertension during pregnancy may be more likely to develop elevation of blood pressure when given oral contraceptives. Hypertension that develops as a result of taking oral contraceptives usually returns to normal after discontinuing the drug. 9. HEADACHE. The onset or exacerbation of migraine or development of headache of a new pattern which is recurrent, persistent, or severe, requires discontinuation of oral contraceptives and evaluation of the cause. 10. BLEEDING IRREGULARITIES. Breakthrough bleeding, spotting, and amenorrhea are frequent reasons for patients discontinuing oral contraceptives. In breakthrough bleeding, as in all cases of irregular bleeding from the vagina, nonfunctional causes should be borne in mind. In undiagnosed persistent or recurrent abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy. If pathology has been excluded, time or a change to another formulation may solve the problem. Changing to an oral contraceptive with a higher estrogen content, while potentially useful in minimizing menstrual irregularity, should be done only if necessary since this may increase the risk of thromboembolic disease. Women with a past history of oligomenorrhea or secondary amenorrhea or young women without regular cycles may have a tendency to remain anovulatory or to become amenorrheic after discontinuation of oral contraceptives. Women with these preexisting problems should be advised of this possibility and encouraged to use other contraceptive methods. Postuse anovulation, possibly prolonged, may also occur in women without previous irregularities. 11. ECTOPIC PREGNANCY. Ectopic as well as intrauterine pregnancy may occur in contraceptive failures. 12. BREAST FEEDING. Oral contraceptives given in the postpartum period may interfere with lactation. There may be a decrease in the quantity and quality of the breast milk. Furthermore, a small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs. The effects, if any, on the breast-fed child have not been determined. If feasible, the use of oral contraceptives should be deferred until the infant has been weaned. **PRECAUTIONS: General:** 1. A complete medical and family history should be taken prior to the initiation of oral contraceptives. The pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen and pelvic organs, including Papanicolaou smear and relevant laboratory tests. As a general rule, oral contraceptives should not be prescribed for longer than one year without another physical examination being performed. 2. Under the influence of estrogen-progestogen preparations, preexisting uterine leiomyomata may increase in size. 3. Patients with a history of psychic depression should be carefully observed and the drug discontinued if depression recurs to a serious degree. Patients becoming significantly depressed while taking oral contraceptives should stop the medication and use an alternate method of contraception in an attempt to determine whether the symptom is drug-related. 4. Oral contraceptives may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention, such as convulsive disorders, migraine syndrome, asthma, or cardiac or renal insufficiency. 5. Patients with a past history of jaundice during pregnancy have an increased risk of recurrence of jaundice while receiving oral contraceptive therapy. If jaundice develops in any patient receiving such drugs, the medication should be discontinued. 6. Steroid hormones may be poorly metabolized in patients with impaired liver function and should be administered with caution in such patients. 7. Oral contraceptive users may have disturbances in normal tryptophan metabolism which may result in a relative pyridoxine deficiency. The clinical significance of this is yet to be determined. 8. Serum folate levels may be depressed by oral contraceptive therapy. Since the pregnant woman is predisposed to the development of folate deficiency and the incidence of folate deficiency increases with increasing gestation, it is possible that if a woman becomes pregnant shortly after stopping oral contraceptives, she may have a greater chance of developing folate deficiency and complications attributed to this deficiency. 9. The pathologist should be advised of oral contraceptive therapy when relevant specimens are submitted. 10. Certain endocrine and liver function tests and blood components may be affected by estrogen-containing oral contraceptives: a. Increased sulfobromophthalein retention. b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability. c. Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered. d. Decreased pregnanediol excretion. e. Reduced response to metyrapone test. **INFORMATION FOR THE PATIENT: (See Patient Package Insert). DRUG INTERACTIONS:** Reduced efficacy and increased incidence of breakthrough bleeding have been associated with concomitant use of rifampin. A similar association has been suggested with barbiturates, phenylbutazone, phenytoin sodium, and ampicillin. **CARCINOGENESIS, PREGNANCY, NURSING MOTHERS: See CONTRAINDICATIONS and WARNINGS. ADVERSE REACTIONS:** An increased risk of the following serious adverse reactions has been associated with the use of oral contraceptives (see WARNINGS): Thrombophlebitis. Pulmonary embolism. Coronary thrombosis. Cerebral thrombosis. Cerebral hemorrhage. Hypertension. Gallbladder disease. Liver tumors. Congenital anomalies. There is evidence of an association between the following conditions and the use of oral contraceptives, although additional confirmatory studies are needed: Mesenteric thrombosis. Neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis. The following adverse reactions have been reported in patients receiving oral contraceptives and are believed to be drug-related: Nausea, usually the most common adverse reaction. Vomiting, occurs in approximately 10% or less of patients during the first cycle. Other reactions, as a general rule, are seen much less frequently or only occasionally. Gastrointestinal symptoms (such as abdominal cramps and bloating). Breakthrough bleeding. Spotting. Change in menstrual flow. Dysmenorrhea. Amenorrhea during and after treatment. Temporary infertility after discontinuance of treatment. Edema. Chloasma or melasma which may persist. Breast changes: tenderness, enlargement, and secretion. Change in weight (increase or decrease). Change in cervical erosion and cervical secretion. Possible diminution in lactation when given immediately postpartum. Cholestatic jaundice. Migraine. Increase in size of uterine leiomyomata. Rash (allergic). Mental depression. Reduced tolerance to carbohydrates. Vaginal candidiasis. Change in corneal curvature (steepening). Intolerance to contact lenses. The following adverse reactions have been reported in users of oral contraceptives, and the association has been neither confirmed nor refuted: Premenstrual-like syndrome. Cataracts. Changes in libido. Chorea. Changes in appetite. Cystitis-like syndrome. Headache. Nervousness. Dizziness. Hirsutism. Loss of scalp hair. Erythema multiforme. Erythema nodosum. Hemorrhagic eruption. Vaginitis. Porphyria. Impaired renal function. (ORTHO-NOVUM 1/50□21 and ORTHO-NOVUM 1/50□28 contain tartrazine. Allergic reactions have been reported with the ingestion of this dye in some patients.) **ACUTE OVERDOSE:** Serious ill effects have not been reported following acute ingestion of large doses of oral contraceptives by young children. Overdosage may cause nausea, and withdrawal bleeding may occur in females.

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Submission of contributions. Manuscripts should in general be sent to a particular Editor according to the following plan: If it is from the southeastern quadrant of the United States or from Canada, or if it has been presented before one of the official sponsoring societies, to Dr. Brewer; if from the northeastern quadrant (including Ohio), or if it is a Clinical Opinion or a Letter to the Editors, to Dr. Zuspan; if from the north central states, any of the United States west of the Mississippi, Hawaii, Alaska, or abroad, to Dr. Quilligan.

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Tables should be typed on separate sheets of paper, not in the text, with one table to a page. They should be numbered in sequence and each must be referred to at an appropriate point in the text. Captions of the tables should be brief, yet indicate clearly the purpose or content of each table. Rows and columns in the table should precisely define the nature of the data in each. Abbreviations in tables should be used as little as possible and if abbreviations are used they should be explained in a footnote to the table.

An abstract of 50 to 150 words, to be published as an introduction, should accompany each manuscript and should be typed on a separate sheet of paper.

A footnote should be included which gives the name and complete mailing address of the person to whom reprint requests and correspondence should be sent.

A Guide to Writing for the American Journal of Obstetrics and Gynecology may be obtained from the Publisher on request.

Illustrations. A reasonable number of halftone illustrations will be reproduced free of cost to the author, but special arrangements must be made with the Editors for color plates, elaborate tables, or extra illustrations. Original drawings or graphs should be drawn with black India ink. Typewritten or freehand lettering is not acceptable. All lettering must be done professionally. **Do not send original art work, x-ray films, or ECG tracings.** Glossy print photographs are preferred, for good black and white contrast is essential.

Announcements. Announcements of meetings must be received by Dr. Brewer at least 2½ months prior to the time of the meeting. Such announcements should concern major meetings and other significant activities. Announcements of symposia or seminars for which fees are charged are not published in the scientific pages of the JOURNAL but may be submitted for paid advertisements, if desired.

Letters to the Editors. A brief Letter to the Editors commenting upon some article which has appeared in the JOURNAL will be considered for publication. The writer of the original article will have an opportunity to reply to unfavorable comments. A brief case presentation of special interest in the form of a Letter to the Editors will also be considered for publication. All such letters should be sent to Dr. Zuspan.

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Estradiol, not estrone, is the logical estrogen to replace

At menopause the normal cyclical production of estradiol declines, resulting for many women in the unpleasant symptoms of estrogen deficiency—hot flushes and atrophic vaginitis being the most common. ESTRACE provides the estradiol the ovary produced in the premenopausal years.

ESTRACE...the orally effective estradiol

Estradiol was long thought desirable in oral estrogen replacement therapy, but administration was not practical owing to erratic absorption. With the technique of micronization, dependable oral absorption has been demonstrated.[3,4]

ESTRACE is rapidly absorbed, active at the cellular level, and follows the normal metabolic pathways in its utilization by the body. ESTRACE provides objective[4] and clinical evidence[3] of ready availability and biologic activity because estradiol can be assayed in plasma.

Easy to titrate to lowest effective dosage

ESTRACE is easy to titrate up or down as necessary for the individual patient to arrive at the lowest effective dose as soon as possible. Available in 1-mg. and 2-mg. *scored* tablets, ESTRACE is usually effective in a single dose of 2 mg. per day, administered on a cyclic basis.

References: 1. Murad F, Gilman AG: Estrogens and progestins, in Goodman L, Gilman A (eds): The Pharmacological Basis of Therapeutics, ed 5. New York, Macmillan Publishing Co, 1975, p 1423.

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See following page for prescribing information.

Mead Johnson
PHARMACEUTICAL DIVISION

ESTRACE® (ESTRADIOL)

Estradiol...the only estrogen necessary in estrogen replacement therapy

1-mg. and 2-mg. scored tablets

Warning

1. ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA. Three independent case control studies have shown an increased risk of endometrial cancer in postmenopausal women exposed to exogenous estrogens for prolonged periods.[1-3] This risk was independent of the other known risk factors for endometrial cancer. These studies are further supported by the finding that incidence rates of endometrial cancer have increased sharply since 1969 in eight different areas of the United States with population based cancer reporting systems, an increase which may be related to the rapidly expanding use of estrogens during the last decade.[4] The three case control studies reported that the risk of endometrial cancer in estrogen users was about 4.5 to 13.9 times greater than in nonusers. The risk appears to depend on both duration of treatment[1] and on estrogen dose.[3] In view of these findings, when estrogens are used for the treatment of menopausal symptoms, the lowest dose that will control symptoms should be utilized and medication should be discontinued as soon as possible. When prolonged treatment is medically indicated, the patient should be reassessed on at least a semiannual basis to determine the need for continued therapy. Although the evidence must be considered preliminary, one study suggests that cyclic administration of low doses of estrogen may carry less risk than continuous administration;[3] it therefore appears prudent to utilize such a regimen. Close clinical surveillance of all women taking estrogens is important. In all cases of undiagnosed persistent or recurring abnormal vaginal bleeding, adequate diagnostic measures should be undertaken to rule out malignancy. There is no evidence at present that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic doses.

2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY. The use of female sex hormones, both estrogens and progestagens, during early pregnancy may seriously damage the offspring. It has been shown that females exposed *in utero* to diethylstilbestrol, a non-steroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare.[5,6] This risk has been estimated as not greater than 4 per 1000 exposures.[7] Furthermore, a high percentage of such exposed women (from 30 to 90 percent) have been found to have vaginal adenosis,[8-12] epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether they are precursors of malignancy. Although similar data are not available with the use of other estrogens, it cannot be presumed they would not induce similar changes. Several reports suggest an association between intrauterine exposure to female sex hormones and congenital anomalies, including congenital heart defects and limb reduction defects.[13-16] One case control study[16] estimated a 4.7-fold increased risk of limb reduction defects in infants exposed *in utero* to sex hormones (oral contraceptives, hormone withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some of these exposures were very short and involved only a few days of treatment. The data suggest that the risk of limb reduction defects in exposed fetuses is somewhat less than 1 per 1000. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well controlled studies that progestagens are effective for these uses. If Estrace® is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus and the advisability of pregnancy continuation.

Clinical Pharmacology — 17β-Estradiol is the most potent physiologic estrogen and, in fact, is the major estrogenic hormone secreted by the human. Estradiol in Estrace® has been micronized and demonstrated to be rapidly and effectively absorbed from the gastrointestinal tract.[17]

Indications: Estrace® is indicated in the treatment of: 1. Moderate to severe *vasomotor* symptoms associated with the menopause. (There is no evidence that estrogens are effective for nervous symptoms or depression which might occur during menopause, and they should not be used to treat these conditions.) 2. Atrophic vaginitis. 3. Kraurosis vulvae. 4. Female hypogonadism. 5. Female castration. 6. Primary ovarian failure. ESTRACE® HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING).

Contraindications: Estrogens should not be used in women (or men) with any of the following conditions: 1. Known or suspected cancer of the breast except in appropriately selected patients with progressing inoperable or radiation resistant disease. 2. Known or suspected estrogen-dependent neoplasia. 3. Known or suspected pregnancy (See Boxed Warning). 4. Undiagnosed abnormal genital bleeding. 5. Active thrombophlebitis or thromboembolic disorders. 6. A past history of thrombophlebitis or thromboembolic disorders associated with previous estrogen use (except when used in treatment of breast or prostatic malignancy).

Warnings: There is now evidence that estrogens increase the risk of carcinoma of the endometrium in humans. (See Boxed Warning.) At the present time there is no evidence that estrogens given to postmenopausal women increase the risk of cancer of the breast. However, women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms should be administered an estrogen with caution and a careful breast examination should be performed. A recent study has reported a 2 to 3-fold increase in the risk of surgically confirmed gall bladder disease in women receiving postmenopausal estrogens.[18] An increased risk of post-surgery thromboembolic complications has been reported in users of oral contraceptives.[19,20] If feasible, estrogen should be discontinued at least 4 weeks before, and not resumed until at least 4 weeks after, surgery of the type associated with an increased risk of thromboembolism. Estrogens should not be used in persons with thromboembolic disorders and they should not be used (except in treatment of malignancy) in persons with a history of such disorders in association with estrogen use or in patients with cerebral vascular or coronary artery disease. Benign hepatic adenoma should be considered in estrogen users having abdominal pain and tenderness, abdominal mass, or hypovolemic shock. Hepato-cellular carcinoma has also been reported in women taking estrogen-containing oral contraceptives.[21] The relationship of this malignancy to these drugs is not known at this time. There is now evidence that elevated blood pressure occurs with use of estrogens in the menopause[22] and blood pressure should be monitored with estrogen use, especially if high doses are used. Diabetic patients taking estrogens should be carefully observed for decrease in glucose tolerance. Estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases.

Precautions: A complete pretreatment and periodic physical examination should be given to estrogen users with special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolaou smear. Conditions which might be influenced by fluid retention such as epilepsy, migraine, and cardiac or renal dysfunction, require careful observation. Certain patients may develop undesirable manifestations of excessive estrogenic stimulation, such as abnormal or excessive uterine bleeding, mastodynia, etc. Patients with a history of depression should be carefully observed. Preexisting uterine fibromyomata may increase in size while using estrogen. The pathologist should be advised of estrogen therapy when relevant specimens are submitted. If jaundice develops in any patient receiving estrogen, the medication should be discontinued while the cause is investigated. Estrogens should be administered with caution in patients with impaired liver function. Estrogens should be used with caution in patients with metabolic bone diseases that are associated with hypercalcemia or in patients with renal insufficiency. Estrogens should be used judiciously in young patients in whom bone growth is not complete. The following endocrine and liver function tests may be affected with larger doses of estrogen: a. Increased sulfobromophthalein retention; b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability; c. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by PBI, T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered; d. Impaired glucose tolerance; e. Decreased pregnanediol excretion; f. Reduced response to metyrapone test; g. Reduced serum folate concentration; h. Increased serum triglyceride and phospholipid concentration. As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk.

Adverse Reactions: The following additional adverse reactions have been reported with estrogenic therapy, including oral contraceptives: Breakthrough bleeding, spotting, change in menstrual flow; Dysmenorrhea; Premenstrual-like syndrome; Amenorrhea during and after treatment; Increase in size of uterine fibromyomata; Vaginal candidiasis; Change in cervical eversion and in degree of cervical secretion; Cystitis-like syndrome; Tenderness, enlargement, secretion of the breasts; Nausea, vomiting; Abdominal cramps, bloating; Cholestatic jaundice; Chloasma or melasma which may persist when drug is discontinued; Erythema multiforme; Erythema nodosum; Hemorrhagic eruption; Loss of scalp hair; Hirsutism; Steepening of corneal curvature; Intolerance to contact lenses; Headache, migraine, dizziness; Mental depression; Chorea; Increase or decrease in weight; Reduced carbohydrate tolerance; Aggravation of porphyria; Edema; Changes in libido.

Overdosage: Serious ill effects have not been reported following the ingestion of large doses of estrogen-containing oral contraceptives by young children. Overdosage of estrogen may cause nausea, and withdrawal bleeding may occur in females.

Dosage and Administration: 1. *Given cyclically for short term use only:* For treatment of moderate to severe *vasomotor* symptoms, atrophic vaginitis, or kraurosis vulvae associated with the menopause. The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible. Administration should be cyclic (e.g., 3 weeks on and 1 week off). Attempts to discontinue or taper medication should be made at 3 to 6 month intervals. The usual initial dosage range is 1 or 2 mg. daily of micronized estradiol adjusted as necessary to control presenting symptoms. The minimal effective dose for maintenanace therapy should be determined by titration.

2. *Given cyclically:* Female hypogonadism; female castration; primary ovarian failure. Treatment is usually initiated with a dose of 1 or 2 mg. daily of micronized estradiol, adjusted as necessary to control presenting symptoms; the minimal effective dose for maintenance therapy should be determined by titration.

Treated patients with an intact uterus should be monitored closely for signs of endometrial cancer and appropriate diagnostic measures should be taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

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How Supplied: Estrace 1 mg; lavender scored tablets, NDC 0087-0755-01, bottles of 100. Estrace 2 mg; turquoise scored tablets, NDC 0087-0756-01, bottles of 100.

Full prescribing information is available in the Estrace physician package insert.

Mead Johnson PHARMACEUTICAL DIVISION

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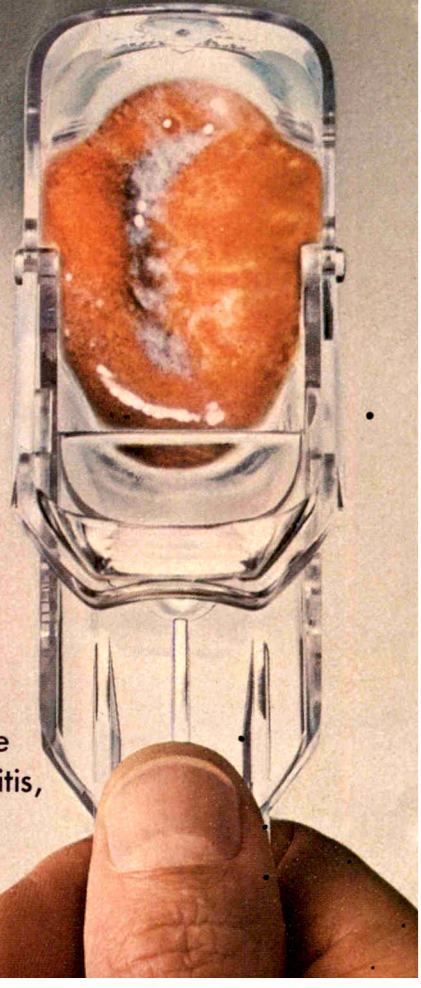
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"Nonspecific" vaginitis is often masked



"Nonspecific" vaginitis

...Often masked by previsit and routine douches, candidiasis and trichomoniasis.[1]

...Often chronic—in a recent clinical study of 5,000 consecutive cases of chronic vaginitis, the chief cause was undiagnosed H. vaginalis vaginitis, followed by candidiasis and trichomoniasis.[1]

1. Fleury, F.J.: Obstet. Gynecol. News 12:1,25, Aug. 15, 1977.
2. Gardner, H.L., and Kaufman, R.H.: Benign Diseases of the Vulva and Vagina, St. Louis, The C.V. Mosby Company, 1969, p. 191.

When you unmask "nonspecific" vaginitis you may find H. vaginalis

Sultrin
TRADEMARK

Triple Sulfa Cream/Vaginal Tablets

effective against H.vaginalis— the cause of over 90% of "nonspecific" vaginitis[2]

Effective
Based on a review by the National Academy of Sciences/National Research Council, SULTRIN was rated as "effective" against *H. vaginalis.*

Prompt symptomatic relief
Patients can experience relief of embarrassing itching and malodorous discharge. Within the same time, most patients can also achieve marked clinical improvement.

Versatile adjunct in other vaginitides
SULTRIN is also effective in treating H.V. vaginitis concomitant with trichomoniasis and candidiasis.

Convenient choice of dosage forms
SULTRIN comes as a soothing, nonstaining and esthetically pleasing cream or convenient vaginal tablets.

Composition: SULTRIN Cream contains sulfathiazole 3.42%, sulfacetamide 2.86%, sulfabenzamide 3.7%, and urea 0.64%. Each SULTRIN Tablet contains sulfathiazole 172.5 mg, sulfacetamide 143.75 mg, and sulfabenzamide 184.0 mg.

Indications: SULTRIN Cream and Tablets are indicated for treatment of *Haemophilus vaginalis* vaginitis. They may also be used as a deodorant for saprophytic infection following radiation therapy.

Contraindications: Sulfonamide sensitivity and kidney disease.

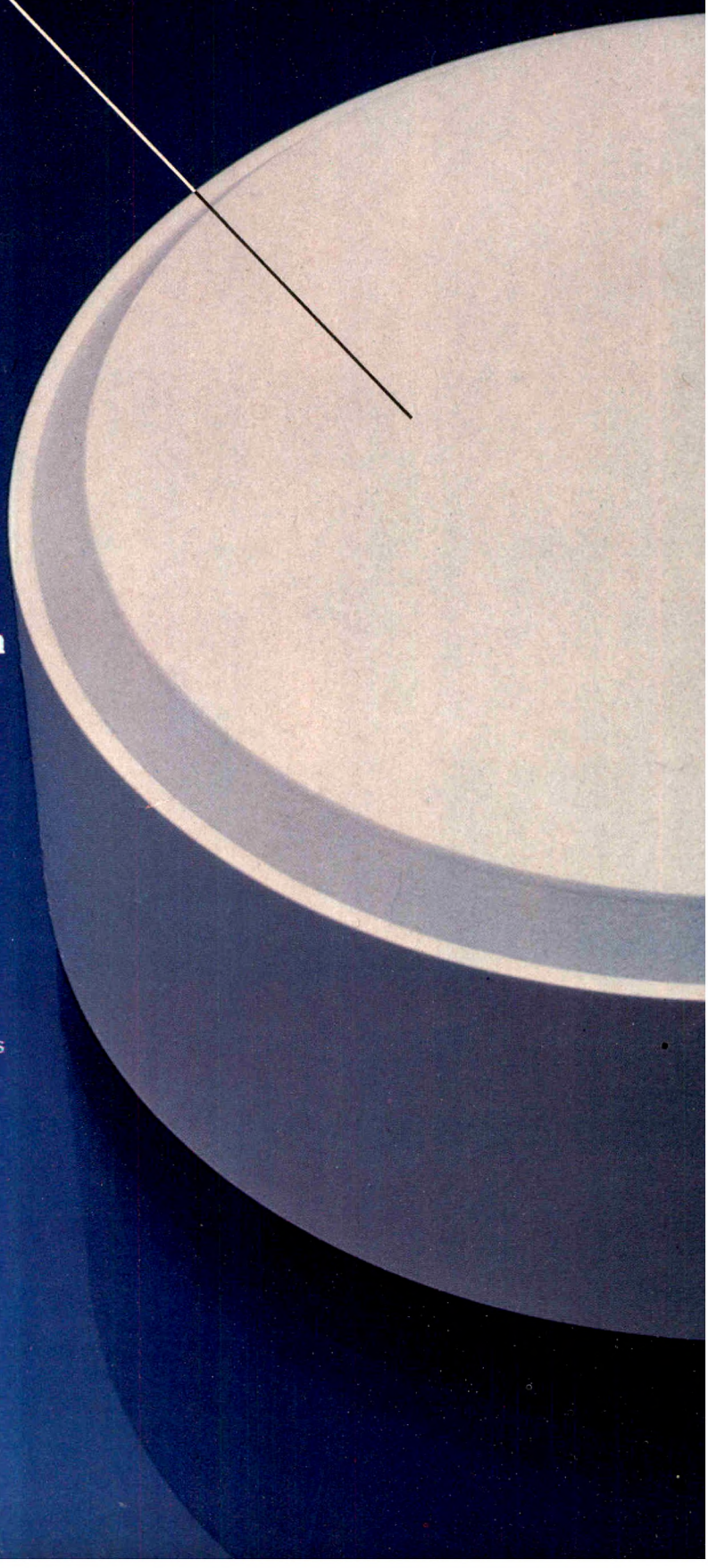
Dosage: SULTRIN Cream: One applicatorful intravaginally twice daily for 4 to 6 days. The dosage may then be reduced one-half to one-quarter.
SULTRIN Tablets: One tablet intravaginally before retiring and again in the morning for ten days. This course may be repeated if necessary.

Supplied: SULTRIN Cream is available in 2.75 oz. (78 g) tubes with the ORTHO* Measured-Dose Applicator.
SULTRIN Tablets are available in packages of 20 foil-wrapped tablets with vaginal applicator.

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The progestogen in oral contraceptives:
But certainly



Norgestrel, the progestogen that distinguishes Ovral and Lo/Ovral.

Today, many physicians are concerned about choosing a suitable estrogen level for their oral contraceptive patients.

The effects of any combination oral contraceptive, however, are largely the result of the synergistic activity between estrogen and progestogen. So it seems wise to choose the progestogen carefully, too.

Norgestrel, the progestogen in Ovral and Lo/Ovral, has many properties worth examining.

Distinctive because it is non-estrogenic and does not add estrogen. Unlike other progestogens in current use, norgestrel has been shown in biological assays to be free from inherent estrogenicity and does not convert to estrogen *in vivo*. So the delicate estrogen-progestogen balance in Ovral and Lo/Ovral remains undisturbed.

It helps maintain a sound endometrium in combination with ethinyl estradiol. Even at very low doses, norgestrel demonstrates a pronounced ability to help support the integrity of the endometrium—a primary function of progestogen in oral contraceptives.

A highly effective estrogen antagonist. Norgestrel displays marked anti-estrogenic activity at the cervical level. It thickens the cervical mucus during the 3-week cycle of therapy and may therefore act as a secondary contraceptive mechanism.



Norgestrel and ethinyl estradiol: together they usually mean patient confidence, comfort and compliance. In separate clinical trials, overall effectiveness with Ovral over an 8 year period was 99.3 percent; with Lo/Ovral over a 4 year period, 99.7 percent.[1] Both Ovral and Lo/Ovral also offered excellent cycle control and a minimum of common side effects.* The drop-out rate due to breakthrough bleeding for Ovral was only 0.5 percent; for Lo/Ovral, only 1.4 percent.

50 mcg Ovral® and 30 mcg Lo/Ovral®: distinguished by norgestrel.

*Serious as well as minor adverse reactions have been reported following the use of all oral contraceptives. The physician should remain alert to their earliest manifestations and in the event of serious adverse reactions, should avoid any oral contraceptives. Contraindications, Warnings, Precautions, Adverse Reactions, etc. in the accompanying IN BRIEF should be carefully considered.

1. Based on life table method.

See important information on following page.

Wyeth Laboratories
Philadelphia, Pa. 19101

OVRAL®
Each tablet contains 0.5 mg norgestrel with 0.05 mg ethinyl estradiol.

LO/OVRAL®
Each tablet contains 0.3 mg norgestrel with 0.03 mg ethinyl estradiol.

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IN BRIEF:

Indications and Usage—OVRAL® and LO/OVRAL® are indicated for the prevention of pregnancy in women who elect to use oral contraceptives (OC's) as a method of contraception.

Contraindications—OC's should not be used in women with any of the following conditions: 1. Thrombophlebitis or thromboembolic disorders. 2. A past history of deep-vein thrombophlebitis or thromboembolic disorders. 3. Cerebral-vascular or coronary-artery disease. 4. Known or suspected carcinoma of the breast. 5. Known or suspected estrogen-dependent neoplasia. 6. Undiagnosed abnormal genital bleeding. 7. Known or suspected pregnancy (see Warning No. 5).

Warnings

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

The use of oral contraceptives is associated with increased risk of several serious conditions, including thromboembolism, stroke, myocardial infarction, hepatic adenoma, gall bladder disease, hypertension. Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks.

1. *Thromboembolic Disorders and Other Vascular Problems:* An increased risk of thromboembolic and thrombotic disease associated with use of OC's is well-established. Three principal studies in Great Britain and 3 in the U.S. have demonstrated increased risk of fatal and nonfatal venous thromboembolism and stroke, both hemorrhagic and thrombotic. These studies estimate that users of OC's are 4 to 11 times more likely than nonusers to develop these diseases without evident cause.

CEREBROVASCULAR DISORDERS—In a collaborative American study of cerebrovascular disorders in women with and without predisposing causes, it was estimated that the risk of hemorrhagic stroke was 2.0 times greater in users than nonusers and the risk of thrombotic stroke was 4 to 9.5 times greater in users than in nonusers.

MYOCARDIAL INFARCTION (MI)—An increased risk of MI associated with use of OC's has been reported, confirming a previously suspected association. These studies, conducted in the UK, found, as expected, that the greater the number of underlying risk factors for coronary-artery disease (cigarette smoking, hypertension, hypercholesterolemia, obesity, diabetes, history of preeclamptic toxemia) the higher the risk of developing MI, regardless of whether the patient was an OC user or not. OC's, however, were found to be a clear additional risk factor. In terms of relative risk, it has been estimated that OC users who do not smoke (smoking is considered a major predisposing condition to MI) are about twice as likely to have a fatal MI as nonusers who do not smoke. OC users who are also smokers have about a 5-fold increased risk of fatal MI compared to users who do not smoke, but about a 10- to 12-fold increased risk compared to nonusers who do not smoke. Furthermore, amount of smoking is also an important factor. In determining importance of these relative risks, however, baseline rates for various age groups must be given serious consideration. Importance of other predisposing conditions mentioned above in determining relative and absolute risks has not as yet been quantified; quite likely the same synergistic action exists, but perhaps to a lesser extent.

RISK OF DOSE—In an analysis of data derived from several national adverse-reaction reporting systems, British investigators concluded that risk of thromboembolism, including coronary thrombosis, is directly related to dose of estrogen in OC's. Preparations containing 100 mcg or more of estrogen were associated with higher risk of thromboembolism than those containing 50-80 mcg. Their analysis did suggest, however, that quantity of estrogen may not be the sole factor involved. This finding has been confirmed in the U.S.

ESTIMATE OF EXCESS MORTALITY FROM CIRCULATORY DISEASES—A large prospective study carried out in the UK estimated the mortality rate per 100,000 women per year from diseases of the circulatory system for users and nonusers of OC's according to age, smoking habits, and duration of use. Overall excess death rate annually from circulatory diseases for OC users was estimated to be 20 per 100,000 (ages 15-34—5/100,000; ages 35-44—33/100,000; ages 45-49—140/100,000), risk being concentrated in older women, in those with long duration of use, and in cigarette smokers. It was not possible, however, to examine interrelationships of age, smoking, and duration of use, nor to compare effects of continuous vs. intermittent use. Although the study showed a 10-fold increase in death due to circulatory diseases in users for 5 or more years, all these deaths occurred in women 35 or older. Until larger numbers of women under 35 with continuous use for 5 or more years are available, it is not possible to assess magnitude of relative risk for this younger group.

Available data from a variety of sources have been analyzed to estimate risk of death associated with various methods of contraception. Estimates of risk of death for each method include combined risk of contraceptive method (e.g. thromboembolic and thrombotic disease in the case of OC's) plus risk attributable to pregnancy or abortion in event of method failure. This latter risk varies with effectiveness of method. The study concluded that mortality associated with all methods of birth control is low and below that associated with childbirth, with the exception of OC's in women over 40 who smoke. Lowest mortality is associated with condom or diaphragm backed up by early abortion. Risk of thromboembolic and thrombotic disease associated with OC's increases with age after about 30 and, for MI, is further increased by hypertension, hypercholesterolemia, obesity, diabetes, or history of preeclamptic toxemia, and especially cigarette smoking.

Physician and patient should be alert to earliest manifestations of thromboembolic and thrombotic disorders (e.g., thrombophlebitis, pulmonary embolism, cerebrovascular insufficiency, coronary occlusion, retinal thrombosis, and mesenteric thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately. A 4- to 6-fold increased risk of postsurgery thromboembolic complications has been reported in OC users. If feasible, OC's should be discontinued at least 4 weeks before surgery of a type associated with increased risk of thromboembolism or prolonged immobilization.

2. *Ocular Lesions*—There have been reports of neuro-ocular lesions such as optic neuritis or retinal thrombosis associated with use of OC's. Discontinue OC's if there is unexplained, sudden or gradual, partial or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal-vascular lesions, and institute appropriate diagnostic and therapeutic measures.

3. *Carcinoma*—Long-term continuous administration of either natural or synthetic estrogen in certain animal species increases frequency of carcinoma of the breast, cervix, vagina, and liver. Certain synthetic progestogens, none currently contained in OC's, have been noted to increase incidence of mammary nodules, benign and malignant, in dogs. In humans, 3 case-control studies have reported an increased risk of endometrial carcinoma associated with prolonged use of exogenous estrogen in postmenopausal women. One publication reported on the first 21 cases submitted by physicians to a registry of cases of adenocarcinoma of the endometrium in women under 40 on OC's. Of cases found in women without predisposing risk factors (e.g., irregular bleeding at the time OC's were first given, polycystic ovaries), nearly all occurred in women who had used a sequential OC. These are no longer marketed. No evidence has been reported suggesting increased risk of endometrial cancer in users of conventional combination or progestogen-only OC's. Several studies have found no increase in breast cancer in women taking OC's or estrogens. One study, however, while also noting no overall increased risk of breast cancer in women on OC's, found an excess risk in subgroups of OC users with documented benign breast disease. Reduced occurrence of benign breast tumors in users of OC's has been well-documented. In summary, there is at present no confirmed evidence from human studies of increased risk of cancer associated with OC's. Close clinical surveillance of all women on OC's is, nevertheless, essential. In all cases of undiagnosed persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be taken to rule out malignancy. Women with a strong family history of breast cancer or with breast nodules, fibrocystic disease, or abnormal mammograms should be monitored with particular care if they elect to use OC's.

4. *Hepatic Tumors*—Benign hepatic adenomas have been found to be associated with use of OC's. One study showed that OC's with high hormonal potency were associated with higher risk than lower potency OC's. Although benign, hepatic adenomas may rupture and may cause death through intra-abdominal hemorrhage. This has been reported in short-term as well as long-term users. Two studies relate risk with duration of use of OC's, the risk being much greater after 4 or more years' use. While hepatic adenoma is rare, it should be considered in women presenting abdominal pain and tenderness, abdominal mass or shock. A few cases of hepatocellular carcinoma have been reported in women on OC's. Relationship of these drugs to this type of malignancy is not known.

5. *Use in or Immediately Preceding Pregnancy, Birth Defects in Offspring, and Malignancy in Female Offspring*—Use of female sex hormones—both estrogenic and progestational agents—during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a nonsteroidal estrogen, have increased risk of developing in later life a form of vaginal or cervical cancer ordinarily extremely rare. This risk has been estimated to be of the order of 1 in 1,000 exposures or less. Although there is no evidence now that OC's further enhance risk of developing this type of malignancy, such patients should be monitored with particular care if they elect to use OC's. Furthermore, 30 to 90% of such exposed women have been found to have epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether this condition is a precursor of vaginal malignancy. Male children so exposed may develop abnormalities of the urogenital tract. Although similar data are not available with use of other estrogens, it cannot be presumed they would not induce similar changes. An increased risk of congenital anomalies, including heart defects and limb defects, has been reported with use of sex hormones, including OC's, in pregnancy. One case-control study estimated a 4.7-fold increase in risk of limb-reduction defects in infants exposed in utero to sex hormones (OC's, hormonal withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some exposures involved only a few days. Data suggest that risk of limb-reduction defects in exposed fetuses is somewhat less than 1 in 1,000 live births. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well-controlled studies that progestogens are effective. There is some evidence that triploidy and possibly other types of polyploidy are increased among abortuses from women who become pregnant soon after ceasing OC's. Embryos with these anomalies are virtually always aborted spontaneously. Whether there is an overall increase in spontaneous abortion of pregnancies conceived soon after stopping OC's is unknown. It is recommended that, for any patient who has missed 2 consecutive periods, pregnancy should be ruled out before continuing OC's. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at time of first missed period, and further use of OC's should be withheld until pregnancy has been ruled out. If pregnancy is confirmed, the patient should be apprised of the potential risks to the fetus, and advisability of continuation of the pregnancy should be discussed. It is also recommended that women who discontinue OC's with intent of becoming pregnant use an alternate form of contraception for a period of time before attempting to conceive. Many clinicians recommend 3 months, although no precise information is available on which to base this. The administration of progestogen-estrogen combinations to induce withdrawal bleeding should not be used as a test of pregnancy.

6. *Gallbladder Disease*—Studies report increased risk of surgically confirmed gallbladder disease in users of OC's and estrogens. In one study, increased risk appeared after 2 years' use and doubled after 4 or 5 years' use. In one of the other studies, increased risk was apparent between 6 and 12 months' use.

7. *Carbohydrate and Lipid Metabolic Effects*—Decrease in glucose tolerance has been observed in a significant percentage of patients on OC's. For this reason, prediabetic and diabetic patients should be carefully observed while on OC's. Increase in triglycerides and total phospholipids has been observed in patients on OC's; clinical significance of this finding remains to be defined.

8. *Elevated Blood Pressure*—Increase in blood pressure has been reported in patients on OC's. In some women, hypertension may occur within a few months of beginning OC's. In the 1st year of use, prevalence of women with hypertension is low in users and may be no higher than that of a comparable group of nonusers. Prevalence in users increases, however, with longer exposure, and in the 5th year of use is 2½ to 3 times the reported prevalence in the 1st year. Age is also strongly correlated with development of hypertension in OC users. Women who previously have had hypertension during pregnancy may be more likely to develop elevation of blood pressure on OC's. Hypertension that develops as a result of taking OC's usually returns to normal after discontinuing the drug.

9. *Headache*—Onset or exacerbation of migraine or development of headache of a new pattern which is recurrent, persistent, or severe, requires discontinuation of OC's and evaluation of the cause.

10. *Bleeding Irregularities*—Breakthrough bleeding, spotting, and amenorrhea are frequent reasons for patients discontinuing OC's. In breakthrough bleeding, as in all cases of irregular vaginal bleeding, nonfunctional causes should be borne in mind. In undiagnosed persistent or recurrent abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy. If pathology has been excluded, time or change to another OC may solve the problem. Changing to an OC with a higher estrogen content, while potentially useful in minimizing menstrual irregularity, should be done only if necessary, since this may increase risk of thromboembolic disease.

Women with past history of oligomenorrhea or secondary amenorrhea or young women without regular cycles may have a tendency to remain anovulatory or to become amenorrheic after discontinuing OC's. Women with these preexisting problems should be advised of this possibility and encouraged to use other methods. Post-use anovulation, possibly prolonged, may also occur in women without previous irregularities.

11. *Ectopic Pregnancy*—Ectopic as well as intrauterine pregnancy may occur in contraceptive failures.

12. *Breast-feeding*—OC's given in the postpartum period may interfere with lactation and decrease quantity and quality of breast milk. Furthermore, a small fraction of the hormones in OC's has been identified in the milk of mothers on OC's; effects, if any, on the breast-fed child have not been determined. If feasible, defer OC's until infant has been weaned.

Precautions—GENERAL—1. A complete medical and family history should be taken prior to initiation of OC's. Pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen and pelvic organs, including Pap smear and relevant laboratory tests. As a general rule OC's should not be prescribed for longer than 1 year without another physical examination.

2. Under influence of estrogen-progestogen preparations, pre-existing uterine leiomyomata may increase in size.

3. Patients with history of psychic depression should be carefully observed and the drug discontinued if depression recurs to a serious degree. Patients becoming significantly depressed while on OC's should stop OC's and use an alternate method to try to determine whether the symptom is drug-related.

4. OC's may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention, such as convulsive disorders, migraine syndrome, asthma, or cardiac or renal insufficiency.

5. Patients with a past history of jaundice during pregnancy have an increased risk of recurrence while on OC's. If jaundice develops, OC's should be discontinued.

6. Steroid hormones may be poorly metabolized in patients with impaired liver function and should be administered with caution.

7. OC users may have disturbances in normal tryptophan metabolism which may result in a relative pyridoxine deficiency. Clinical significance is undetermined.

8. Serum folate levels may be depressed by OC's. Since the pregnant woman is predisposed to development of folate deficiency and incidence of folate deficiency increases with increasing gestation, it is possible that if a woman becomes pregnant shortly after stopping OC's, she may have a greater chance of developing folate deficiency and complications attributed to this deficiency.

9. The pathologist should be advised of OC therapy when relevant specimens are submitted.

10. Certain endocrine- and liver-function tests and blood components may be affected by estrogen-containing OC's: a. Increased sulfobromophthalein retention. b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability. c. Increased thyroid-binding globulin (TBG) leading to increased circulating total-thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered. d. Decreased pregnanediol excretion. e. Reduced response to metyrapone test.

Information for the Patient—See Patient Package Labeling.

Drug Interactions—Reduced efficacy and increased incidence of breakthrough bleeding have been associated with concomitant use of rifampin. A similar association has been suggested with barbiturates, phenylbutazone, phenytoin sodium, and ampicillin.

Carcinogenesis—See Warnings on carcinogenic potential of OC's.

Pregnancy—Category X. See Contraindications, Warnings.

Nursing Mothers—See Warnings.

Adverse Reactions—An increased risk of these serious adverse reactions has been associated with use of OC's (see Warnings): thrombophlebitis, pulmonary embolism, coronary thrombosis, cerebral thrombosis, cerebral hemorrhage, hypertension, gallbladder disease, benign hepatomas, congenital anomalies. There is evidence of an association between the following conditions and use of OC's although additional confirmatory studies are needed: mesenteric thrombosis, neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis.

The following adverse reactions have been reported in patients on OC's and are believed to be drug-related. Nausea and/or vomiting, usually the most common adverse reactions, occur in approximately 10 percent or less of patients during the first cycle. Other reactions, as a general rule, are seen much less frequently or only occasionally. Gastrointestinal symptoms (such as abdominal cramps and bloating); breakthrough bleeding, spotting, change in menstrual flow; dysmenorrhea, amenorrhea during and after treatment, temporary infertility after discontinuance of treatment; edema; chloasma or melasma which may persist; breast changes: tenderness, enlargement, and secretion; change in weight (increase or decrease); change in cervical erosion and cervical secretion; possible diminution in lactation when given immediately postpartum; cholestatic jaundice; migraine; increase in size of uterine leiomyomata; rash (allergic); mental depression; reduced tolerance to carbohydrates; vaginal candidiasis; change in corneal curvature (steepening), intolerance to contact lenses.

The following adverse reactions have been reported in users of OC's, and the association has been neither confirmed nor refuted: premenstrual-like syndrome, cataracts, changes in libido, chorea, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption, vaginitis, porphyria.

Acute Overdose—Serious ill effects have not been reported following acute ingestion of large doses of OC's by young children. Overdosage may cause nausea, and withdrawal bleeding may occur in females.

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OBSTETRICS

Evaluating student performance in an obstetrics and gynecology clerkship

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The development of a comprehensive evaluation system for an obstetrics and gynecology clerkship at the University of Utah is described and the results of two years experience using it are presented. Seven different measurement procedures were developed and used with 111 junior medical students including pre- and post-tests, oral examination, clinical performance ratings by residents, and ratings by faculty on oral and written presentations and participation in tutorial sessions. Learning gains as measured by pre-post test scores were significant at the 0.001 level. Only six of 37 correlations among the evaluation measures were significantly related at the 0.01 level; furthermore, little relationship could be found between measures of student achievement in cognitive as compared to clinical skill areas. The need for multiple sources of information on student performance in clerkships is discussed (AM. J. OBSTET. GYNECOL. 134:235, 1979.)

DURING clinical clerkships, medical students are expected to apply a broad fund of knowledge to specific problems of patients, to interact skillfully with them, and to master basic technical skills. This integration of knowledge, skills, and attitudes about patient care occurs in a variety of clinical and classroom settings under the tutelage of numerous different personnel (e.g., attendings, house staff, nurses, social workers, etc.). Under such circumstances, accurate appraisal of student competence is both complex and difficult. The question arises: is it necessary to obtain information on student performance from multiple sources? If so, what type of evaluation measures are needed? Some reports of clerkship evaluation systems have described parts of an evaluation program,[1–4] while others have outlined untested general models.[5–6] This paper describes the development and assessment of a comprehensive evaluation system for a junior clerkship in obstetrics and gynecology at the University of Utah. Data on 111 medical students enrolled in this six-week clerkship between September, 1975, and February, 1977, are analyzed to address the following questions:

1. Did students increase their level of knowledge in obstetrics and gynecology during the clerkship?

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Table I. Pearson correlations among nine measures of student clinical performance (N = 111)

Measures of performance	*Pre-test*	*Post-test*	*University preceptor*	*Community preceptor*	*Presentation*	*Paper*	*Oral exam*	*University residents*
Post-test	0.3219*							
University preceptor	0.0893	−0.0783						
Community preceptor	0.1382	0.0922	0.075[illegible]					
Presentation	0.1371	0.0576	0.157[illegible]	−0.0174				
Paper	0.0086	0.0257	0.063[illegible]	0.0253	0.1644			
Oral examination	0.2293†	0.1984	0.196[illegible]	0.1181	−0.0240	−0.0584		
University residents	0.0318	−0.0238	0.295[illegible]*	−0.0237	0.2889†	0.1533	0.1166	
Community residents	0.1133	0.0344	0.0433	0.1290	0.0658	−0.1198	0.2359†	0.3388*

*Significant at $p < 0.001$.
†Significant at $p < 0.01$.

2. What are the relationships among nine different measures of student performance?
3. What is the relationship between cognitive measures and clinical skill measures of student performance?

Evaluation design

In order to develop an effective clerkship evaluation system, the clerkship curriculum was first analyzed and then revised. In 1970, a modified competence-based curriculum was introduced into the basic obstetrics and gynecology clerkship at the University of Utah. Five areas of competence, a series of learning activities, and evaluation procedures were identified by the faculty.

The clerkship consisted of two three-week rotations at the University Hospital and a community hospital. Learning activities included: ward, clinic, operating room, and delivery room experiences; faculty preceptorships; conferences; grand rounds; self-learning programs; and student presentations.

To evaluate student achievement in the five competency areas, seven different measurement procedures were developed. These included: pre- and post-tests and oral examination, ratings of clinical performance by residents, ratings of an oral and written presentation, and ratings by faculty of student participation in tutorial meetings.

The pre- and post-tests were designed to measure knowledge gains. The tests were identical, consisting of 50 multiple choice questions, and were administered on the first and last days of the clerkship. The oral examination, which evaluated the student's ability to apply knowledge and solve clinical problems, was taken immediately following the post-test. Faculty rated student responses to the oral examination on a four-item rating scale.

Evaluation of student ability to investigate a topic in obstetrics and gynecology and to present the information in a logical and coherent fashion was assessed by faculty using a six-item rating scale. It was completed by faculty for both formal presentations and papers.

Clinical performance on the wards and in other clinical situations was assessed by residents at the end of both three-week rotations. Residents at each hospital (three at the University and three at the community hospital) met as a group and pooled their observations into one rating form for each hospital rotation. The clinical performance form consisted of a 27 item rating scale with general comments.

The didactic teaching sessions focused on case workups and problem solving. Student participation in these sessions was evaluated by faculty using a five-item rating scale. Each student received two evaluations of clinical performance by residents and two evaluations for tutorial sessions by faculty (one from each hospital).

All of these evaluation measures were used to determine the level of student achievement except the pre-test. The percentage contribution of each element to the student's total grade was: 20% post-test, 20% oral examination, 10% paper, 10% presentation, 20% clinical rating by residents, and 20% preceptor rating.

After developing the new curriculum and evaluation models, the entire system was implemented in 1975. Data on student performance in the clerkship from 1975 to 1977 were analyzed using a correlated t test to measure differences between pre- and post-test scores and the Pearson Correlation Coefficient to examine relationships among the seven types of ratings and between measures of cognitive ability and clinical skills.

Results

Pre- and post-tests were administered to determine the degree of knowledge gain during the clerkship. Using a correlated t test to compare pre-test scores (mean = 53.19, SD 7.08) with post-test scores (mean = 76.42, SD 6.49), differences were found which were significant at the 0.001 level.

Seven different evaluation forms were used to assess student achievement in the clerkship. Since two of these forms (clinical performance and preceptor rat-

ings) were completed at both hospitals, nine sources of information were available for analysis. Table I reports Pearson correlation coefficients for the nine measures. Six out of 37 correlations were significant at the $p < 0.01$ level.

The strongest correlations were between resident ratings at University and community hospitals ($r = 0.3389$), between pre- and post-tests ($r = 0.3219$), and between preceptors and residents at University Hospital ($r = 0.2958$). Each of these correlations were significant at the 0.001 level.

Three other correlations were significant at the 0.01 level. These were between resident ratings at the University and student presentations ($r = 0.2889$), between oral exam and resident ratings at the University Hospital ($r = 0.2359$), and between the oral examination and pre-test ($r = 0.2293$).

The association of cognitive ability and clinical skills was examined by dividing the nine evaluative measures into two groups: (1) cognitive measures: pre- and post-tests, oral examination, presentation, and paper; and (2) clinical skills: preceptor and resident ratings at each hospital. The Pearson correlation coefficient between these two sets of measures was low ($r = 0.1539$) and nonsignificant.

Comment

This study was a pilot effort to examine the application of a comprehensive evaluation system to a clinical clerkship. The evaluation program was designed to assess student knowledge, skills, and attitudes through the use of seven different instruments. Analysis of student performance in the clerkship over a two-year period revealed low correlation between the nine measures of student achievement and between cognitive and noncognitive measures. This suggests that high performance in one area of the clerkship (e.g., oral examination) is not necessarily related to high performance in another area (e.g., clinical performance). The strength of this evaluation system is its ability to sample a broad range of student behavior and to balance several performance measures to form the final grade.

Limitations of this evaluation program include the use of identical forms for pre- and post-tests, the expense of employing a large number of measurement procedures, and the lack of demonstrated reliability. The need for a variety of measures is apparent but the number and type of measures are open to debate. While logical arguments were developed as rationale for each measurement procedure, faculty have subsequently determined that writing proficiency was not a critical clerkship objective and, therefore, the paper and its accompanying rating form were deleted.

While costly, a comprehensive evaluation system based on multiple sources of information is necessary in order to accurately evaluate student achievement. In light of increasing pressure for objective evaluation of educational programs and certification of professional competence, further efforts at designing and analyzing clerkship evaluation systems are essential.

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A comparison of clindamycin-gentamicin and penicillin-gentamicin in the treatment of post–cesarean section endomyometritis

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A random comparison of clindamycin-gentamicin (C-G) and penicillin-gentamicin was made in 200 women who developed endomyometritis following cesarean section. All pretreatment profiles indicated similar populations. The clinical response was more favorable in the women receiving clindamycin-gentamicin. The implications of these results upon clinical practice is discussed. (AM. J. OBSTET. GYNECOL. 134:238, 1979.)

THIS STUDY presents a new therapeutic approach to post–cesarean section endomyometritis, the most serious problem of hospital-acquired infection for the obstetrician-gynecologist. Recently, the most popular focus of interest has been preventive antibiotics. Although the strategy of prophylaxis reduces febrile morbidity, it has not avoided the development of serious infections. A widely used alternative approach has been to employ penicillin and an aminoglycoside for the treatment of infected patients, reserving agents effective against *Bacteroides fragilis* for those women who remained febrile. The present study compared this commonly used regimen to clindamycin-gentamicin, which provides superior coverage of *Bacteroides fragilis*. This study design avoids prophylaxis for all patients undergoing cesarean section, restricting antibiotic usage to those patients with infection.

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Table I. Primary indications for cesarean section

Indication	*Clindamycin-gentamicin*	*Penicillin-gentamicin*
Breech	31*	34†
Failure to progress in labor	30‡	29
Previous cesarean section, in labor	24‡	18
Fetal distress	9	11‡
Transverse lie	3	3‡
Placenta previa	3	3
Abruptio placentae	0	2
Total	100§	100§

*Five patients in this category were delivered of twins.
†Four patients in this population were delivered of twins.
‡One patient in this group was delivered of twins.
§Total twins: clindamycin-gentamicin, 7; penicillin-gentamicin, 6.

Material and methods

Between February, 1976, and October, 1977, all women undergoing cesarean section at the Los Angeles County–University of Southern California (LAC-USC) Medical Center were eligible for the study. Prophylactic antibiotics for cesarean section were not employed. Women who had a clinical diagnosis of postpartum uterine infection based upon the presence of fever and uterine tenderness received on a random basis, either

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Table II. Pretreatment patient profile

Characteristic	*Clindamycin-gentamicin*	*Penicillin-gentamicin*
Total patient population (No.)	100	100
Racial composition (No.):		
Mexican-American	88	81
Black	9	9
Caucasian	2	8
Oriental	0	2
American Indian	1	0
Age (yr.) (mean ± SD)	25.2 ± 5.8	25.13 ± 5.55
Maternal weight (kg) (mean ± SD)	69.3 ± 12.3	69.5 ± 11.5
Previous pregnancy history (No.):		
Para 0	36	41
Mean parity	1.67	1.24
Fetal weight (g) (mean ± SD)	3,203 ± 684.3	3,308.1 ± 710
Status of membranes and monitoring (No.)		
Membranes intact, not monitored	34	35
Membranes ruptured, not monitored	19	11
Membranes ruptured, monitored	47	54
Mean time of membrane rupture	9.25 hr.	12.03 hr.
Mean time of monitoring	5.08 hr.	5.77 hr.
Meconium	8	10
Bacteremia at onset of therapy (No.)	23	25

penicillin-gentamicin or clindamycin-gentamicin. Five million units of penicillin was administered intravenously every six hours. Also 600 mg of clindamycin was given intravenously at 6 hour intervals. Gentamicin, 80 mg, was given intravenously at 8 hour intervals. In a few instances, the gentamicin dosage was 60 mg and occasionally the route of administration was intramuscular. In most cases, an oral form of penicillin or clindamycin was given after the patient had been afebrile for 24 to 48 hours to complete 10 days' treatment. The gentamicin was continued for the length of hospitalization. In the patients who failed to respond to initial therapy, by a continued febrile course, therapeutic decisions to prescribe additional antibiotics or heparin or perform a second operation were made by the physician team. There were a number of patient exclusions. Patients allergic to penicillin or those who received antibiotics during labor or in the recovery room were not entered into the study. Those patients started on the protocol who were subsequently found to have a urine bacterial colony count of greater than 100,000/cc from the specimen obtained prior to therapy were excluded to avoid the possibility of evaluating a patient whose primary site of infection might be the urinary tract. In addition, there were wide variations in the number of women recruited for the study, depending upon the interest of the senior resident responsible for the service. The majority of patients were enrolled in the study when one of the first two authors rotated through the obstetric service.

Before therapy, blood, urine, and endometrial cultures taken through the cervix were obtained. No attempt was made to utilize a sheathed system for the endometrial specimen and neither special gassed tube nor anaerobic jar inoculation was performed. Tests of renal and liver function were obtained prior to and during therapy.

A number of evaluations were performed to assess the patient's response to therapy. The two populations were analyzed to see if similar risk factors existed prior to treatment. The clinical response was assessed after 6 weeks or more had elapsed to determine the number of women who required additional antibiotics, heparin, or operative care before a cure was achieved. A fever index, a quantitative measure in degree hours of the patient's response to therapy, was measured in all of the study population.

Results

The indications for cesarean section of the two populations are listed in Table I. There were no significant differences noted between the two groups.

The pretreatment patient profile and risk factors of the two populations are listed in Table II. The documentation of the length of labor was too incomplete to permit analysis. Membranes were ruptured for a longer interval in the penicillin-gentamicin group than in the clindamycin-gentamicin group. Although there is a difference, it is not statistically significant. In addition, Fig. 1 demonstrates no correlation between the length of time of membrane rupture and severity of infection as noted by a fever index.

Bacterial isolates were obtained in 48 patients from blood cultures. In the case of isolates considered contaminants, both culture bottles had to have a positive growth.[1] In 29 of the 48 episodes (60.4%), anaerobes

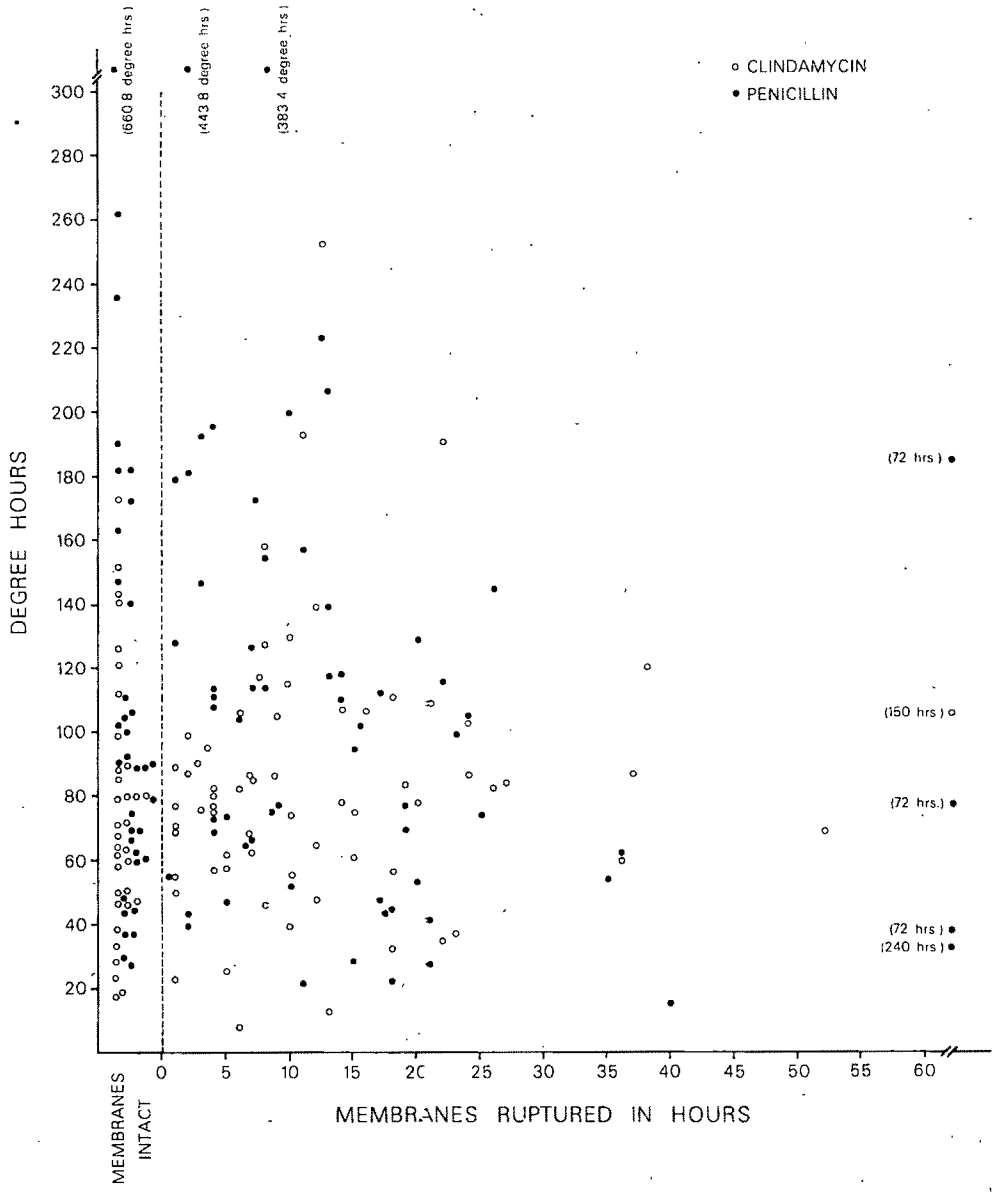


Fig. 1. A scattergram of the patient's febrile response compared to the length of time of membrane rupture.

were isolated. Twelve of the episodes, five with penicillin-gentamicin and seven with clindamycin-gentamicin, involved only the organisms diphtheroids and *Propionibacterium acnes* and may have been contaminants.

The clinical response to therapy is noted in Table III. Most of the evaluations favor the clindamycin-gentamicin regimen. There were fewer problems in this population of women throughout the analysis with statistical significance as noted in Table III.

Comment

The response to clindamycin-gentamicin therapy of post–cesarean section infection was superior to the more commonly employed penicillin-aminoglycoside regimen. This difference is not related to the selection of different patient populations as measured by the indications for cesarean section (see Table I) or pretreatment risk factors (see Table II). We were concerned about the similarity of the two populations when we first viewed the data on the length of time of membrane rupture for we were aware that the frequency of maternal infection increases with the duration of membrane rupture.[2] However, statistical analysis revealed no difference in the two populations. More important, no correlation in this study could be found between the duration of membrane rupture and the

Table III. Comparison of the two regimens

	Clindamycin-gentamicin	*Penicillin-gentamicin*	*Significance*
No. of patients	100	100	N.S.
Therapy completed, no problems	86	64	$p < 0.001$
Poor clinical results:			
No response—third antibiotic	5	29	$p < 0.001$
Abdominal wound infection	8	16	N.S.
Operative drainage only	6	4	N.S.
Prolonged febrile course after drainage	2	12	$p < 0.02$ (Fisher's exact test)
Serious problems:	0	4	$p < 0.06$
Pelvic abscess, total abdominal hysterectomy, bilateral salpingo-oophorectomy	0	1	
Wound evisceration	0	1	
Heparin	0	2	
Reaction during antibiotics:	4	3	N.S.
Rash	2*	2	
Hematuria	0	1†	
Diarrhea	2	0	
Indirect measures of morbidity:			
Hospital days	7.4	8.7	$p < 0.01$ (Mann-Whitney U test)
Fever index in degree hours			
Median	77.3	91.3	$p < 0.02$
Mean	81.2	110.7	
±SD	±40.6	±89.6	
±SE	± 4.06	± 9.0	

N.S. = Not significant.
*Drug continued, rash disappeared, one patient.
†Drug continued, hematuria stopped.

severity of infection following cesarean section (see Fig. 1). There was a better clinical response in the women who received clindamycin (see Table III). Fewer women required a third antibiotic, fewer serious wound infections developed, and no patient had a dehiscence or required heparin or a second operation.

This therapeutic combination regimen offers clear advantages over the reported prophylactic antibiotic regimens. Although febrile morbidity has been reduced with preventive antibiotics, serious postoperative pelvic infections have still been reported. In this study, the treatment of symptomatic women with clindamycin-gentamicin prevented the progression to serious infection. Whether this result will always be seen will be determined by more observations on a larger number of patients. This regimen avoids the administration of potent antibiotics to all women undergoing cesarean section as well as to the fetus in utero if the antimicrobial drugs are given preoperatively.

Since the results of this study differ from a prior comparison of these two antibiotic regimens,[3] some comment is necessary. There is a striking difference in the patient population of the two studies. In the current evaluation, all patients were seen early in the course of the disease. In the earlier study, some patients had more advanced disease when they were enrolled in the comparison.

The population of women who develop an infection following cesarean section has parallels with the animal model of infection developed by Weinstein and associates.[4] Serious pelvic infection manifested by early-onset sepsis or late-onset abscess formation can occur after the initiating event of a cesarean section in an operative field contaminated by bacteria. The timing of antibiotic administration seems critical. If there is a delay in the use of antibiotics that are particularly effective against anaerobes, serious late infectious complications occur in the human and the rat.

The risk-benefit ratio of the clindamycin-gentamicin regimen has not been established. The majority of the patients treated with penicillin-gentamicin had uncomplicated courses, and the results are remarkably similar to those reported by Gibbs and associates[5] in which serious problems were seen in only 4% of those originally treated with a combination of penicillin-kanamycin. However, serious problems occurred in a few patients who received this combination initially and these were not seen in the clindamycin-gentamicin group. In the current study, there was little toxicity associated with the use of clindamycin. The drug was discontinued in only three patients receiving the initial regimen, one for a rash and in two instances for diarrhea. There were no cases of pseudomembranous enterocolitis. In other geographic locations with different patient populations, more frequent diarrhea or enterocolitis might negate the apparent therapeutic benefit of this combination regimen. Continued experience with this regimen should clarify this point.

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Effects of magnesium sulfate treatment on perinatal calcium metabolism

I. Maternal and fetal responses

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Serial maternal and cord blood determinations of the ions and hormones involved in calcium homeostasis were made in pre-eclamptic women treated with intravenous magnesium sulfate. A 4 gm loading dose followed by 1 to 2 gm/hr caused maternal serum magnesium concentrations to rise 150%, to levels of 3.3 to 4.5 mEq/L, and ionized calcium levels to fall 16%, to 1.89 mEq/L. The hypocalcemia evoked a 35% increase in maternal parathyroid hormone concentration without significantly altering calcitonin. Changes in total calcium paralleled those of ionized calcium; phosphorus levels were not affected by magnesium infusion. At the time of delivery the offspring of these women were hypermagnesemic and relatively hypocalcemic, although less so than their mothers. Fetal ionized calcium levels, although lower with magnesium treatment than in control subjects, were within the lower limits of the normal range, which perhaps explains why the fetus did not respond with increased PTH or decreased calcitonin output. These results indicate that the principal maternal response to magnesium-induced hypocalcemia involves increased parathyroid hormone secretion which tends to preserve maternal calcium homeostasis, while the fetus is partially protected from hypermagnesemia and hypocalcemia by the placenta. (AM. J. OBSTET. GYNECOL. 134:243, 1979.)

PARENTERAL magnesium sulfate has been the mainstay of the therapy of pre-eclampsia and eclampsia for many years. Given to prevent maternal seizures, the drug acts principally by antagonizing the action of calcium at the myoneural junction.

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Magnesium is intimately involved with calcium homeostasis. Hypermagnesemia depresses serum calcium levels, and some have suggested that this is due to interference with the synthesis or release of parathyroid hormone.[1] Maternal hypocalcemia following therapy with magnesium sulfate has been described.[2] Modest degrees of magnesium deficiency lead to elevations of serum calcium and parathyroid hormone,[3] and more profound hypomagnesemia has been shown to cause hypocalcemia. This too has been postulated as being due to interference with the synthesis or release of parathyroid hormone[4–6] or secondary to magnesium-induced end-organ unresponsiveness.[7]

Magnesium ions cross the placenta[8] and an apparent depression in serum calcium has been reported in fetuses of mothers treated with magnesium sulfate.[9] While some adverse effects on the offspring of these patients have been reported,[10] their occurrence is quite rare.[11]

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Table I. Maternal concentrations of ions and calcium-regulating hormones (mean ± S.D.)

	Baseline			*At delivery*			*End of infusion*		
	Treated (n = 15)	*Control (n = 11)*	*Sig.*	*Treated*	*Control*	*Sig.*	*Treated*	*Control*	*Sig.*
Magnesium (mEq/L)	1.42 ±0.11	1.36 ±0.12	N.S.	3.56 ±0.41	1.31 ±0.11	$p < 0.001$	3.29 ±0.83	1.31 ±0.08	$p < 0.001$
Ionized calcium (mEq/L)	2.24 ±0.06	2.29 ±0.08	N.S.	1.97 ±0.17	2.23 ±0.09	$p < 0.001$	1.89 ±0.16	2.28 ±0.08	$p < 0.001$
Total calcium (mEq/L)	4.41 ±0.19	4.55 ±0.21	N.S.	4.07 ±0.31	4.41 ±0.22	$p < 0.01$	3.75 ±0.28	4.51 ±0.21	$p < 0.001$
Parathyroid hormone (μl-Eq/ml)	4.46 ±0.81	5.97 ±1.16	$p < 0.01$	6.02 ±1.37	6.53 ±1.26	N.S.	5.87 ±1.51	6.54 ±1.74	N.S.
Calcitonin (pg/ml)	225 ±64	209 ±48	N.S	207 ±65	247 ±73	N.S.	188 ±67	225 ±24	N.S.
Phosphorus (mg/dl)	4.70 ±1.51	3.94 ±0.58	N.S.	4.48 ±1.80	3.77 ±0.79	N.S.	4.69 ±1.60	4.16 ±0.36	N.S.
Albumin (gm/dl)	3.13 ±0.33	3.04 ±0.23	N.S.	3.06 ±0.38	3.03 ±0.22	N.S.	2.53 ±0.34	2.76 ±0.30	N.S.

Table II. Percent change from baseline, mean maternal values

	At delivery		*At end of infusion (controls = 24 hr after delivery)*		*24 hr after end of infusion, treated*
	Treated	*Control*	*Treated*	*Control*	
Magnesium	+150.7***	−3.7	+131.7***	−3.7	+2.8
Ionized calcium	−12.1***	−2.6	−15.7***	0	0
Total calcium	−7.7**	−3.1	−15.0***	−0.1	−0.5
Parathyroid hormone	+34.9**	+9.4	+31.6**	+9.5	+3.6
Calcitonin	−8.0	+18.2	−16.5	+7.6	−21.1
Phosphorus	−4.7	−4.3	0	+5.6	−2.5
Albumin	−2.3	0	−19.2***	−9.2*	−15.0*

Significance: *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. All others not significant.

The purpose of this study was to investigate the effects of intravenous magnesium sulfate therapy on the ions and hormones involved in calcium homeostasis in the mother and fetus.

Materials and methods

Fifteen women with pre-eclampsia were treated with intravenous magnesium sulfate. A loading dose of 4 gm administered over 30 minutes was followed by a maintenance dose of 1 gm (12 patients) or 2 gm (3 patients) per hour. The infusion was continued through labor and for 24 hours after delivery in each patient. The control group consisted of 11 patients (10 normotensive, one hypertensive) infused with dextrose-water or dextrose-saline solutions during abor. Treated and control groups were similar with regard to age (19.2 vs. 21.1 years), parity (0.7 vs. 1.2), duration of gestation (38.9 vs. 38.3 weeks), and mean infant birth weight (3,330 vs. 3,540 grams). The mean interval from entry into the study until delivery was 10 hours (range 4 to 30) in treated subjects and 8 hours (range 2 to 12) in control subjects.

Serum levels of magnesium (Mg), ionized calcium (Ca^{++}), total calcium (Ca), parathyroid hormone (PTH), albumin, and phosphorus (P) and plasma levels of calcitonin (CT) were measured in serial samples of maternal blood and in umbilical arterial (UA) and venous (UV) blood at delivery. The final maternal blood samples in the treated group were obtained 24 hours after cessation of magnesium sulfate therapy, and in the control group 24 hours after delivery.

Baseline samples were collected on all patients and, after the infusion was begun, blood was withdrawn at 15, 30, 60, 120, and 240 minutes, and then every 4 to 6 hours. Blood for determination of Mg, Ca^{++}, Ca, PTH, albumin, and P was collected from an indwelling forearm vein catheter into plain vacuum tubes. UA and UV blood for these determinations was collected by puncture of the vessels in the clamped and cut cord, prior to delivery of the placenta. The blood was allowed to clot at room temperature for 1 hour, and centifuged at 3,000 rpm for 15 minutes. To preserve anaerobic conditions, serum for Ca^{++} determination was withdrawn via needle through the rubber stopper

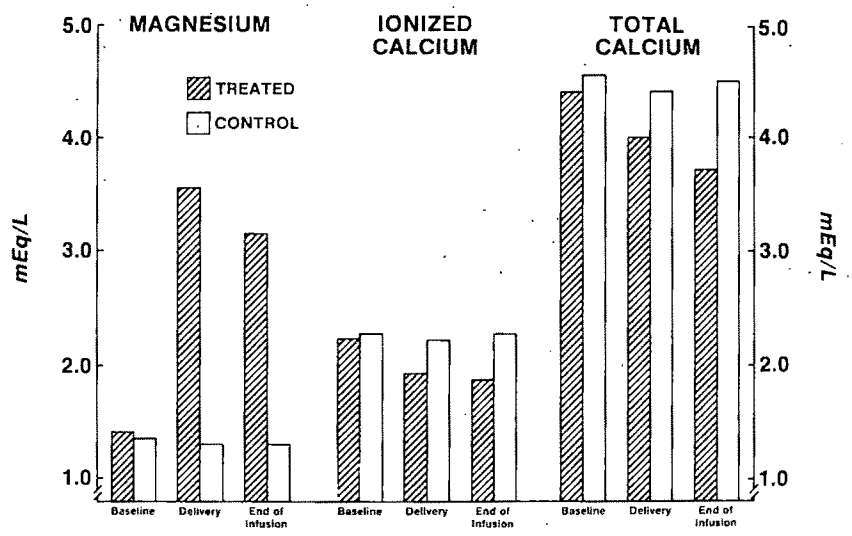


Fig. 1. Mean maternal serum levels of magnesium and ionized and total calcium at baseline, the time of delivery, and the end of the magnesium sulfate infusion.

into a syringe which was immediately capped and sealed. Specimens for determination of Mg, Ca^{++}, Ca, and P were either analyzed immediately or stored frozen for up to 72 hours, previous experiments in our laboratory having demonstrated their stability for at least this period of frozen storage. Serum for PTH determination was frozen, and that for albumin refrigerated, until assayed. Blood for CT determinations was collected into heparinized vacuum tubes, transported to the laboratory in ice, centrifuged in cold immediately, and the plasma separated and frozen until assayed.

Serum Ca^{++} activity was measured on duplicate samples with a calcium flow-through electrode (Orion model 801), Ca and Mg concentrations by atomic absorption spectrophotometry (Perkin-Elmer model 303), and P by the colorimetric method of Fiske and Subbarow.[12] Serum total protein was measured by a modification[13] of the biuret reaction with serum blanks, and the albumin fraction was determined by cellulose acetate electrophoresis (Beckman System R-100 Paper Electrophoresis Analyzer).

Serum PTH was measured by a modification described in detail elsewhere[14] of the RIA method of Arnaud, Teso, and Littledike,[15] utilizing guinea pig antibovine PTH antiserum, purified bovine PTH (Wilson Laboratories, lot 147865) tracer, and dilutions of a pool of human parathyroid tissue culture medium as standards. The assay detects as little as 0.5 microliter-equivalents (μlEq) of standard human parathyroid tissue culture medium per milliliter of serum, and its normal range in adult human beings is 3.76 to 8.56 μlEq/ml.

Plasma CT was measured by a slight modification of the method of Sizemore and associates,[16] with the use of goat antihuman synthetic CT antiserum and human synthetic CT (N.V. Organon, batch SC 30) for tracer and standards. The assay detects as little as 5 pg of CT per milliliter of plasma, and its normal basal range in adult human subjects is 55 to 380 pg/ml.

The assays for both PTH and CT involved measurements at three dilutions of each serum or plasma sample.

Informed consent was obtained from all patients. This project had the prior approval of the Committee on Research Involving Human Subjects.

Results

Maternal.

Magnesium. Baseline values of serum Mg were the same in treated and control patients (Table I). By the time of delivery, mean Mg levels in treated patients were 151% greater than baseline preinfusion values (Table II), rising from 1.42 ± 0.11 to 3.56 ± 0.41 mEq/L, whereas Mg levels in control patients at delivery were unchanged. At the end of the magnesium infusion, the mean Mg level in the treated group was 3.29 ± 0.83 mEq/L, 132% greater than baseline values, whereas control patients 24 hours after delivery had a mean Mg level unchanged from baseline (Fig. 1). Serum Mg levels in treated patients had returned to normal 24 hours after cessation of the magnesium infusion.

The most rapid change in serum Mg levels occurred in the first hour of magnesium sulfate infusion (which included the 4 gm loading dose), during which mean

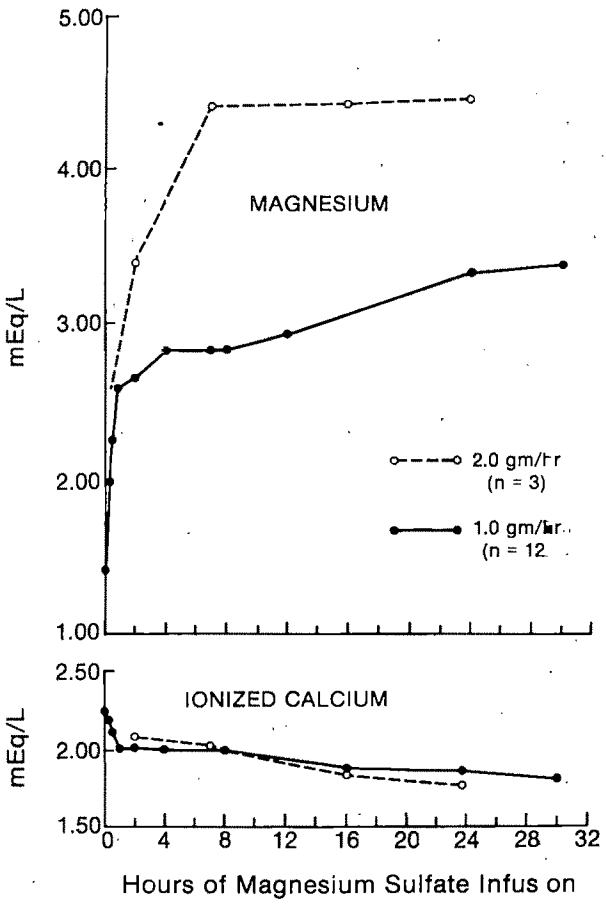


Fig. 2. Mean maternal serum magnesium and ionized calcium concentrations during magnesium sulfate infusions of 1 and 2 gm/hr.

values increased 78%, from 1.42 to 2.57 mEq/L (Fig. 2). During the maintenance dose of 1 gm/hr there was then a more gradual rise to maximum mean levels of 3.33 mEq/L (135% greater than baseline) at 24 hours, after which levels remained relatively constant until the end of the infusion. At a maintenance dose of 2 gm/hr, serum Mg levels rose to a maximum at 6 to 8 hours of 4.47 mEq/L, after which the levels remained fairly constant until the infusion was stopped or the rate of infusion reduced. Thus, with both dosage regimens there was a plateau at which presumably the rate of infusion equalled the rate of excretion, and after this point serum Mg levels did not rise further. This point was reached earlier (6 vs. 24 hours) with the higher (2 gm/hr) infusion rate.

The maximum serum level of Mg achieved was dependent on the *rate* of infusion. At the end of the infusion, there was no statistically significant correlation between either the change in Mg levels vs. the total dose of magnesium sulfate administered ($r = 0.40$) or the change in Mg vs. the hours of infusion ($r = 0.06$). However, the change in Mg levels correlated significantly with the average rate (grams per hour) of infusion ($r = 0.684$, $p < 0.005$).

Ionized calcium. In control subjects, ionized calcium levels remained constant throughout labor, delivery, and the first 24 hours after delivery (Tables I and II). Ca^{++} in magnesium sulfate–treated subjects fell 12.1% by the time of delivery and 15.7% by the end of the infusion (Fig. 1). Both of these changes are highly significant ($p < 0.001$).

As with the rise in serum Mg, the fall in Ca^{++} was most rapid during the first hour of magnesium infusion (Fig. 2), when it fell 11% below baseline values. Following this there was a gradual but continuous decline until the end of the infusion. The percent fall in Ca^{++}, and the absolute levels reached, were the same in patients receiving 1 or 2 gm/hr of magnesium sulfate.

There was no significant correlation between the change in Mg levels and the change in Ca^{++} levels, either at the time of delivery ($r = 0.27$) or at the end of the infusion ($r = 0.32$). However, unlike the situation with serum Mg levels, by the end of the infusion there was significant correlation between the change in serum Ca^{++} and the total dose of magnesium received ($r = 0.65$, $p < 0.01$), and between the change in serum Ca^{++} and the duration of magnesium infusion ($r = 0.51$, $p < 0.05$).

Total calcium. The changes in total calcium paralleled those in ionized calcium in control subjects, in whom there was no significant change from baseline values, and in treated patients, in whom total Ca fell 7.7% ($p < 0.01$) by the time of delivery and 15.0% ($p < 0.001$) by the end of the infusion.

Parathyroid hormone. As indicated in Table I, preinfusion PTH levels in pre-eclamptic subjects were significantly lower than corresponding values in control subjects (4.46 ± 0.81 vs. 5.97 ± 1.16 μlEq/ml, $p < 0.01$). However, in control subjects there was no significant change in PTH levels throughout labor or the early puerperium, whereas PTH levels rose significantly in treated subjects (Table II). Mean PTH levels in treated patients increased 34.9% above baseline by the time of delivery and 31.6% by the end of the infusion, both statistically significant increases ($p < 0.01$). In the three patients infused with 2 gm/hr mean PTH levels increased 54% by the time of delivery. By 24 hours after the end of infusion, PTH levels had returned to baseline values (Table II).

Calcitonin. Plasma CT levels in treated patients fell by an average of 8.0% at the time of delivery and 16.5% by

Table III. Maternal-fetal relationships at delivery (mean ± S.D.)

	Maternal vein			*Umbilical vein*			*Umbilical artery*		
	Treated (n = 15)	*Control (n = 11)*	*Sig.*	*Treated (n = 15)*	*Control (n = 11)*	*Sig.*	*Treated (n = 11)*	*Control (n = 8)*	*Sig.*
Magnesium (mEq/L)	3.56 ±0.41	1.31 ±0.11	$p < 0.001$	3.33 ±1.03	1.49 ±0.18	$p < 0.001$	3.32 ±0.95	1.52 ±0.18	$p < 0.001$
Ionized calcium (mEq/L)	1.97 ±0.17	2.23 ±0.09	$p < 0.001$	2.62 ±0.20	2.73 ±0.17	N.S.	2.59 ±0.14	2.75 ±0.20	$p < 0.05$
Total calcium (mEq/L)	4.07 ±0.31	4.41 ±0.22	$p < 0.01$	5.29 ±0.31	5.22 ±0.24	N.S.	5.22 ±0.22	5.20 ±0.32	N.S.
Parathyroid hormone (μlEq/ml)	6.02 ±1.37	6.53 ±1.26	N.S.	5.69 ±1.15	7.30 ±1.41	$p < 0.01$	5.71 ±1.79	5.91 ±2.19	N.S.
Calcitonin (pg/ml)	207 ±65	247 ±73	N.S.	228 ±64	273 ±92	N.S.	243 ±71	270 ±45	N.S.
Phosphorus (mg/dl)	4.48 ±1.80	3.77 ±0.79	N.S.	6.57 ±1.35	6.05 ±0.83	N.S.	6.41 ±1.60	6.12 ±1.00	N.S.
Albumin (gm/dl)	3.06 ±0.38	3.03 ±0.22	N.S.	3.79 ±0.47	3.54 ±0.48	N.S.	3.89 ±0.41	3.46 ±0.30	$p < 0.05$

the end of the magnesium sulfate infusion, whereas mean CT levels increased somewhat in control patients (Tables I and II). However, there was great variability in the CT response in both treated and control patients, and thus none of the differences in CT concentration between treated and control patients, or among treated patients before and during magnesium infusion, was statistically significant.

Phosphorus. There was no significant change in serum P during magnesium sulfate infusion, nor were there any significant differences between treated and control subjects at any time during the study period (Tables I and II).

Albumin. Baseline serum albumin concentrations were similar in treated (3.13 ± 0.33 gm/dl) and control (3.04 ± 0.23 gm/dl) subjects. Furthermore, at the time of delivery, there was no significant difference in albumin concentrations between treated and control subjects, and there had been no significant change from baseline values within either group (Tables I and II).

However, by the end of the infusion, serum albumin concentration in the treated group had fallen 19.2% ($p < 0.001$), whereas levels in control subjects had fallen 9.2% at 24 hours after delivery ($p < 0.05$).

Maternal-fetal relationships at delivery. Relationships between maternal and umbilical blood studies are shown in Table III. In control subjects, Mg levels in umbilical blood exceeded those in the mother, whereas in treated patients umbilical blood Mg levels, although more than twice as great as control cord blood levels, were lower than those in maternal venous blood. The ratio of fetal to maternal mean Mg levels was 1.07 in control subjects and 0.87 in treated cases, indicating that the transplacental magnesium gradient was reversed with magnesium treatment.

Ionized calcium was 4.2% lower in UV and 6.2% lower in UA in treated than in control subjects, but the depression of Ca^{++} in the fetus was not as great as that in maternal blood of treated subjects.

UV and UA total calcium levels were the same in treated and control subjects, despite the fact that maternal venous Ca levels were 8.4% lower in treated subjects.

PTH levels were lower in the cord blood of treated compared with control subjects, with the difference statistically significant in UV but not in UA.

Calcitonin levels did not differ significantly in treated and control subjects, in either maternal or fetal blood.

Phosphorus levels in fetal blood exceeded those in maternal, in both treated and control subjects. There was, however, no significant difference between treated and control groups in either maternal or fetal phosphorus levels.

Maternal serum albumin concentrations at delivery were essentially identical in treated and control subjects. The fetuses of treated patients had significantly higher albumin concentrations than those of control subjects in UA (but not in UV) serum.

Comment

Maternal response. Maternal serum magnesium levels rise to levels two to three times normal with magnesium sulfate infusions of 1 to 2 gm/hr. With either dosage regimen a plateau is reached, presumably when the rate of infusion equals that of urinary excretion. This plateau occurs at 24 hours (3.33 mEq/L) in patients treated with 1 gm/hr, and much sooner and at a higher level (6 to 8 hours, 4.47 mEq/L) in those receiv-

ing 2 gm/hr. Once the plateau level is reached, the magnesium levels appear to be unaffected by the total dose or duration of treatment, but only by the rate of infusion. This effect is especially obvious in our data by the end of the magnesium sulfate infusion. It is less apparent at delivery, because a number of patients treated with the lower dose had not reached the plateau level by the time of delivery.

This report represents the first systematic study of serum Mg levels with intravenous magnesium sulfate treatment, and it is interesting to note that the values attained with infusions of a 4 gm loading dose followed by 1 gm/hr are slightly below the "therapeutic range" (3.5 to 7 mEq/L) described by Pritchard[17] with intramuscular administration of the drug. The efficiency of the intravenous regimen in preventing seizures suggests that therapeutic levels may not be as high as previously defined for the intramuscular route.

Magnesium treatment clearly depresses maternal ionized calcium levels, and it must be emphasized that the magnitude of the fall in Ca^{++} is indeed remarkable. Serum Ca^{++} is normally regulated within a very narrow range. Pitkin and Gebhardt[18] found normal serum Ca^{++} in late pregnancy to be 2.24 ± 0.06 mEq/L (mean ± S.D.). Assuming the normal range to be described by mean ± 2 S.D., the fall in Ca^{++} caused by magnesium sulfate infusion can be seen to be quite large—the change between baseline and delivery values represents a fall of 4.5 S.D. and that between baseline and the end of the magnesium infusion a fall of nearly 6 S.D. The levels to which Ca^{++} fell correlated directly with the duration of magnesium sulfate treatment and the total dose of magnesium given. A correlation could not be demonstrated, however, between the absolute levels of Mg and Ca^{++} achieved. Most likely, a direct relationship between these two parameters was not found because each is influenced by other variables, serum Mg chiefly by urinary excretion and Ca^{++} mainly by PTH secretion. The modulating effects of PTH on Ca^{++} are probably the reason that the fall in serum Ca^{++} was the same in patients treated with 1 or 2 gm/hr of magnesium sulfate, despite the fact that those treated with 2 gm/hr achieved higher serum Mg levels.

The observed changes in total calcium levels are related to changes in ionized calcium (which accounts for about 50% of total calcium) and in albumin (to which nonionized calcium is bound). In treated patients at delivery, the 12% fall in ionized calcium (induced by magnesium sulfate) accounts for a 6.0% fall in total calcium, whereas the remaining 1.7% fall in total calcium is due to the 2.3% drop in serum albumin. Likewise at the end of the infusion, the 15.7% drop in ionized calcium accounts for a 7.9% fall in total calcium, whereas the remainder is due to the 19.2% fall in serum albumin. The more marked fall in serum albumin in treated patients compared to control subjects is probably due to the intravascular volume contraction of these pre-eclamptic patients at the beginning of infusion and the quantities of intravenous fluid used in therapy, as well as the marked mobilization of extracellular fluid which occurs after delivery.

The mechanism through which hypermagnesemia induces a fall in serum ionized calcium remains unclear, but the significant PTH response demonstrated by treated subjects in this study suggests some mechanism other than suppression of parathyroid gland function, which some have proposed.[1, 19]

PTH levels increased promptly and substantially in association with magnesium-induced falls in serum Ca^{++} concentration, and this increased hormone secretion clearly represents a protective response against even greater degrees of hypocalcemia. While symptomatic maternal hypocalcemia as a complication of magnesium sulfate therapy has been described,[2] its rarity reflects the efficacy of the parathyroid gland in maintaining calcium homeostasis.

CT acts to reduce serum Ca^{++}, and it is interesting to speculate that the observed depression of maternal CT levels in magnesium-treated subjects is a response to the fall in Ca^{++}. Because of the large variation in CT response within both the treated and control groups, however, statistical significance cannot be ascribed to this fall in maternal CT and it seems unlikely that CT is involved in the homeostatic response to hypermagnesemia.

Maternal-fetal relationships. The observed maternal-fetal relationships at delivery indicated a "protective" effect of the placenta in modulating the effects of altered maternal Mg and Ca^{++} on fetal levels. Thus, although cord blood levels of Mg were increased in treated patients, the proportionate increase was not as great in fetal as in maternal blood. Likewise the reduction of fetal serum Ca^{++} was not as great as the fall in maternal levels.

Despite the relative hypocalcemia of the fetuses in the treated group, they did not respond by increasing PTH output, fetal PTH levels in treated patients being lower than in control subjects. This would seem to indicate that the fetal parathyroid is relatively suppressed, similar to the situation which has been described in neonates.[20, 21] However, our finding of cord PTH levels (both control and treated) within the normal adult range speaks against parathyroid suppression and more in favor of a lack of normal adult responsiveness.

Likewise, the fetus did not seem to respond to hypocalcemia by suppressing CT production, fetal CT levels being the same in treated and control subjects.

The apparently higher PTH concentrations in UV than UA of control subjects might give the impression that PTH crosses the placenta, but this is known not to occur.[22–24] However, this difference is more apparent than real, for statistically the difference between control UV and UA PTH levels was not significant ($p > 0.05$).

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Human polymorphonuclear leukocyte phagocytosis in pregnancy

Development of inhibition during gestation and recovery in the postpartum period

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The phagocytosis of *S. aureus* by normal human PMN leukocytes was inhibited by pregnancy serum. Control sera from normal adult nulliparous women, from men, and from cord blood all functioned normally in support of phagocytosis. However, particle ingestion was reduced significantly ($p < 0.001$) when leukocytes were in 15% pregnancy serum obtained at term. To determine at what stage in pregnancy the inhibition of phagocytosis could first be detected, sera were obtained from multiple pregnant donors and pooled according to week of gestation. Significantly fewer bacteria were ingested in each of the serum pools obtained after week 16 of pregnancy and the inhibitory effect persisted through gestation. Following delivery, less inhibition was detected as early as 2 days post partum. Phagocytosis assays were performed in six matched maternal and cord serum pairs. Five of the six maternal sera showed inhibition of phagocytosis; one pregnancy and all cord sera functioned normally in support of bacterial ingestion by normal granulocytes. Since neutrophils are essential to the development of rheumatoid arthritis and certain other inflammatory disorders, the subsidence of these diseases during gestation and their exacerbation post partum could be related, at least in part, to the inhibitory effects of pregnancy serum on leukocyte functions. (AM. J. OBSTET. GYNECOL. 134:250, 1979.)

ALTHOUGH MOST of the observations presented thus far have been retrospective, it is generally accepted that many rheumatic and other inflammatory disorders subside during pregnancy.[1, 2] The exact nature of the factor or factors responsible for this amelioration of disease activity is unknown, but adrenocorticosteroids, estrogenic or progestational hormones, and pregnancy-related serum proteins have all been considered.[1] We have presented evidence that pregnancy serum depresses some of the functions of normal polymorphonuclear (PMN) leukocytes.[3, 4] These alterations of neutrophil functions could provide an explanation for the subsidence of inflammatory processes during gestation. We sought to determine whether the inhibitor of phagocytosis detected in pregnancy paralleled the clinical amelioration of arthritis during gestation and its exacerbation post partum. Sera obtained at various intervals throughout the course of gestation and after delivery were studied for their effects on neutrophil phagocytosis. The results presented in this paper show a close correlation between the effects of pregnancy serum on cellular functions and disease activity and could provide an explanation for remissions of inflammatory disorders during gestation.

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Materials and methods

PMN leukocyte isolation. Venous blood obtained from healthy male adults was anticoagulated with heparin and red blood cells sedimented with the addi-

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tion of 6% dextran-saline. The leukocyte-rich plasma was collected, centrifuged at 270 × g for 15 minutes in the cold, and the white blood cell (WBC) pellet was washed in Hanks' buffer containing 0.01% bovine serum albumin and 150 mg/dl of dextrose. This buffer was used in all experiments. Approximately 75 to 80% of the isolated cells were PMN and more than 95% were viable as determined by trypan blue dye exclusion. Leukocytes from three or more individuals were pooled and cell concentrations were adjusted to 5×10^6 WBC/ml.

Serum pools. Serum was obtained from women with uncomplicated, untreated, intrauterine pregnancy at various intervals throughout gestation and pooled at each 2 to 4 week interval of pregnancy. The pool from women less than 12 weeks pregnant contained only two individual serum samples. Each of the following pools contained three or more individual sera: 12 to 16 weeks, 16 to 18 weeks, 18 to 22 weeks, 22 to 26 weeks, 26 to 30 weeks, 30 to 34 weeks, 34 to 38 weeks, and at delivery. Sera were also obtained following uncomplicated deliveries in unmedicated women at 2 day intervals for the first week post partum and every 2 weeks thereafter until the sixth week. Normal serum pools were prepared from healthy male and from healthy female donors. The normal female serum pool was obtained from nulliparous adults who had never received oral contraceptives. A cord serum pool was obtained from umbilical cord bloods following the second stage of uncomplicated labor. Each pool contained serum from eight or more donors. All experiments utilizing human bloods were approved by the local human experimentation committee. Serum pools were stored at −76° C until studied. Only sterile sera without bactericidal activity for the organism studied were utilized.

Bacteria. A fresh growth of *Staphylococcus aureus* grown on trypticase soy agar was used for phagocytosis studies. Organisms were diluted so that the bacteria : WBC ratio was 5 : 1.

Phagocytosis assay. Into sterile plastic tubes were placed 0.5 ml of the WBC suspension, 0.15 ml of the serum to be studied, and 0.15 ml of buffer. These normal leukocytes were preincubated in the serum at 37° C for 30 minutes with gentle mixing prior to the addition of 0.2 ml of the bacterial suspension. The final serum dilution was 15%. Following rapid mixing with bacteria, tubes were capped, rotated end-over-end at 30 rpm in a 37° C 5% CO_2 water-jacketed incubator, and at various time intervals aliquots were removed for analysis of phagocytosis. Glass slides were smeared and stained and 300 PMN leukocytes per slide were counted. The number of cells clearly containing at least one microorganism was quantitated. Previous studies[3] indicated that 30 minutes of incubation was a representative time for assay and this period was used in the data presented in this paper.

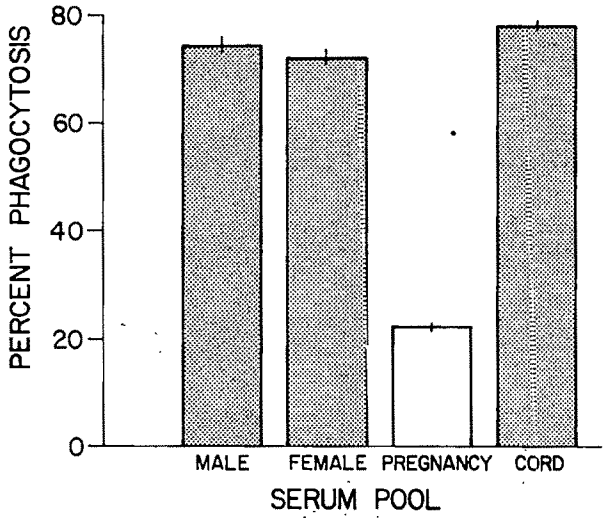


Fig. 1. Effect of various serum pools on the phagocytosis of viable *S. aureus* by normal PMN leukocytes. The pregnancy pool was obtained from eight donors, each 36 to 40 weeks pregnant. All sera were studied at 15% dilution in Hanks' BSS. The percent of neutrophils containing one or more organisms was determined after 30 minutes' incubation. Shown are the means ± 1 S.E.M. for two experiments, each with several replicates. Significantly fewer ($p < 0.001$) normal PMN leukocytes had ingested bacteria in pregnancy serum than in any of the other serum pools studied.

Statistical analysis. Significance was determined with Student's t test. Data are presented as the means ± S.E.M. derived from numerous experiments, each with multiple replicates.

Results

The effect of various human serum pools on the phagocytosis of viable *S. aureus* by normal human neutrophils is shown in Fig. 1. Following preincubation of cells in serum for 30 minutes at 37° C, bacteria were added and phagocytosis was measured after 30 minutes' incubation. Prompt and efficient phagocytosis was supported by the male, the female, and the cord serum pools. In each case in these experiments, over 70% of PMN leukocytes contained ingested bacteria. However, significantly fewer neutrophils contained intracellular microorganisms when the phagocytes were suspended in 15% pregnancy serum ($p < 0.001$). This difference was seen when pregnancy serum was contrasted with either the male, the female, or the cord serum pools. Leukocyte viability was not altered by any of the sera studied, and none was bactericidal.

In separate experiments, individual sera obtained during labor were contrasted with matched umbilical

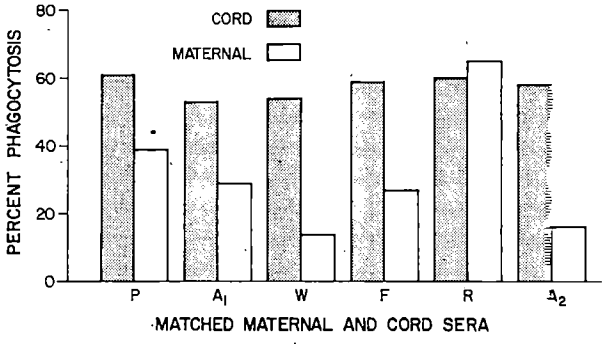


Fig. 2. Phagocytosis of viable *S. aureus* by normal neutrophils in matched pregnancy and cord sera. Serum was obtained from six individuals during labor and from matched umbilical cords after the second stage of labor. Each pair was simultaneously studied at 15% dilution. Time of incubation was 30 minutes.

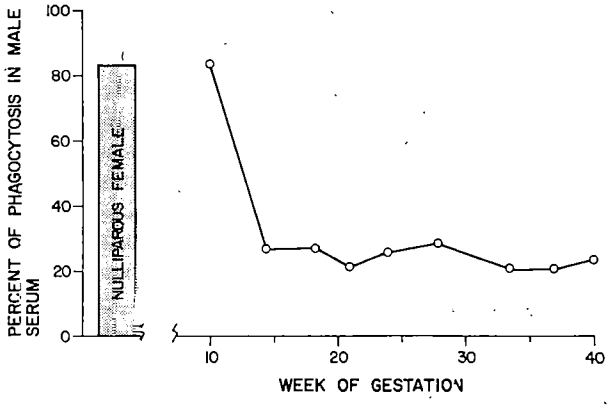


Fig. 3. Effect of sera obtained throughout gestation on the phagocytosis of *S. aureus* by normal human PMN leukocytes. The percentage of normal neutrophils ingesting one or more organisms in 15% male serum was set as 100% activity. The normal female serum pool was obtained from nulliparous females who had never taken oral contraceptives. Sera from multiple pregnant donors were pooled according to week of gestation and studied simultaneously for their effect on *S. aureus* uptake by normal neutrophils. See text for details.

cord sera. The results for six sets of matched sera are shown in Fig. 2. Phagocytosis by normal neutrophils was supported by each of the cord sera. In these experiments over 50% of PMN leukocytes contained one or more organisms. However, in five of the six matched sera studied, there was inhibition of bacterial ingestion by the maternal serum. One pregnancy serum, maternal serum R, did not inhibit phagocytosis. The matched set R was studied a second time and again phagocytosis was normal in both the cord and maternal sera.

To determine at what stage in pregnancy the inhibition of phagocytosis could first be detected, sera were obtained from multiple pregnant donors and pooled according to week of gestation. Phagocytosis in an adult male serum pool was established as the normal control. A serum pool derived from nulliparous women who had never received oral contraceptive medications was simultaneously studied at an identical dilution and served as a second control. In these experiments, the percent of normal PMN leukocytes ingesting microorganisms in the nulliparous female pool was 83% of that in the male serum pool. Serum obtained in the first 16 weeks of gestation did not inhibit phagocytosis. However, significantly fewer bacteria were ingested in each of the serum pools obtained after week 16 of pregnancy, the inhibitory effect persisting from the 16 to 18 week pool throughout gestation (Fig. 3).

After delivery, the inhibition of phagocytosis seen throughout pregnancy rapidly disappeared. Sera obtained from multiple donors at various time intervals post partum showed a return toward normal support of phagocytosis as early as 2 days after delivery (Fig. 4). All sera were contrasted with the effect of a male serum pool. Additional controls were a pregnancy pool obtained between 36 and 40 weeks of gestation and a nulliparous female pool. Thus, serum from pregnancy donors after 16 weeks' gestation inhibits phagocytosis by normal neutrophils. This suppressive effect persists throughout gestation but returns toward normal several days post partum.

Comment

We have previously documented that the phagocytosis of both viable and heat-killed *S. aureus* by normal human neutrophils is significantly diminished in the presence of pregnancy serum.[3, 4] Differential studies involving either leukocytes obtained from pregnant or control subjects, when suspended in either pregnancy or control serum pools, indicated that the inhibition was due to a humoral and not a cellular factor. Intracellular metabolic events occurring after ingestion, including bacterial killing and nitroblue tetrazolium reduction, were decreased in proportion to the number of particles ingested. These findings suggested that the active serum component exerted its inhibitory action at the surface of the PMN leukocyte.[4]

In this paper we present evidence that the inhibitory action of pregnancy serum on neutrophil functions can be detected as early as weeks 16 to 18 of gestation. The serum specimens obtained prior to week 16 supported prompt and efficient ingestion and did not differ from any of the controls studied. Pregnancy serum obtained after 16 weeks, however, suppressed phagocytosis and this inhibitory action persisted throughout the remainder of gestation. Shortly after delivery, postpartum

serum was found to support phagocytosis in a more efficient manner. The marked inhibitory activity detected during pregnancy was greatly diminished as early as 2 days after delivery.

Six pairs of matched maternal and cord sera were studied simultaneously and contrasted with control serum. Five of the six pregnancy sera obtained at the time of delivery contained the inhibitor but, interestingly, one (maternal serum R) did not. This finding suggested that the serum suppressor developed in most but not all pregnancies. In addition, it was apparent that cord serum supported phagocytosis as well as normal adult serum pools, indicating that the inhibitor present during gestation did not cross the placenta.

The nature of the humoral constituent responsible for this suppression of phagocytosis is not yet known with certainty. In previous studies we have shown the inhibitor to be heat stable and nondialyzable.[3] The possible role of hydrocortisone was also investigated. The data obtained indicated that cortisol in the pregnancy serum pool was not responsible for the inhibition of granulocyte functions observed.[4] Hydrocortisone, in vitro, in amounts exceeding by fivefold the concentration in pregnancy serum did not inhibit ingestion. In addition, the level of inhibition of phagocytosis detected in individual pregnancy sera did not correlate with their cortisol concentrations. Previous authors have failed to show an inhibition of phagocytosis by the in vivo administration of steroid.[5, 6] In more recent experiments, we have localized the active inhibitory component to a large-molecular-weight protein fraction isolated with Sephadex G-200 chromatography. Preliminary experiments have suggested that the inhibitor has physical-chemical characteristics resembling the pregnancy zone protein (PZP) described by von Schoultz and Stigbrand[7] and by Straube and coworkers.[8] Further confirmatory experiments must, however, be done.

This demonstration of diminished neutrophil activity during gestation and restoration of normal function post partum closely parallels the course of rheumatoid arthritis and several other inflammatory disorders during pregnancy. The amelioration of inflammatory joint disease is usually apparent in the first trimester in most, but not all, individuals and arthritis recurs by 6 weeks

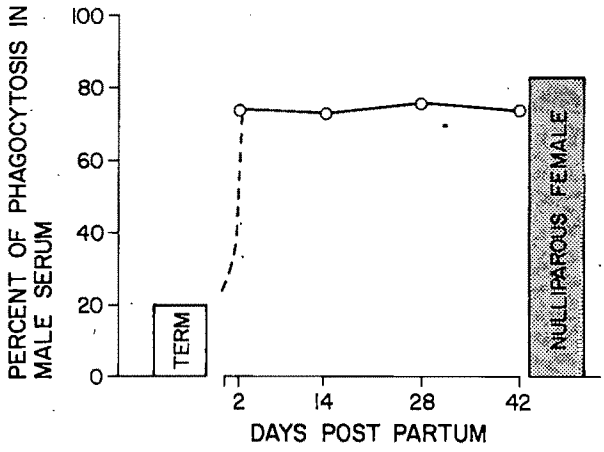


Fig. 4. Disappearance of pregnancy serum inhibition of phagocytosis post partum. Sera were obtained from multiple donors at various time intervals post partum, diluted to 15%, and contrasted with the effect of male serum (100% activity), term pregnancy serum, and nulliparous female serum pools on the ingestion of *S. aureus* by normal human neutrophils.

post partum in 50%.[2] Since neutrophils are essential to the development of synovitis in rheumatoid arthritis, their suppression by pregnancy serum could account for this improvement; the disappearance of the suppressor post partum could then lead to the disease exacerbation usually observed. Thus, the timing of the development of the suppressor closely parallels the clinical observation of rheumatoid arthritis. It is of interest that not all of the sera obtained during pregnancy inhibited phagocytosis. One of the six matched maternal-cord pairs did not suppress bacterial ingestion by normal neutrophils. A further parallel is recognized with rheumatoid arthritis in that only approximately 75% of patients with rheumatoid arthritis will report amelioration of their arthritis during gestation.[1, 2] The ultimate characterization of the neutrophil inhibitor and its quantitation in the serum of patients with rheumatoid arthritis in a prospective manner would provide the essential information required. The final elucidation of the pregnancy regulator would provide additional clues to the mechanisms responsible for the alteration of inflammation during gestation and could suggest new avenues for therapeutic intervention.

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Suppression of mixed lymphocyte reaction by progesterone and estradiol-17β

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The effects of estrone, estradiol-17β, estriol, testosterone, progesterone, and 20α-dihydroprogesterone on incorporation of ^{3}H-thymidine into cultured lymphocytes from normal men and nonpregnant women in response to allogeneic stimulation was investigated with two-way MLR. A dose-dependent reduction in the mean percent incorporation was observed in the range of progesterone concentration between 2×10^3 and 10^4 ng/ml with statistically significant differences from the control cultures. Estradiol-17β at 10^4 ng/ml produced a slight but significant inhibition of incorporation. No significant change in incorporation occurred with the other steroids tested. Since the suppressive property of progesterone in phytohemagglutinin-induced lymphocyte culture reported in our previous communication was reproduced by the present investigation in MLR, the possible role of progesterone in immunoregulation during pregnancy is emphasized as has been postulated previously. (AM. J. OBSTET. GYNECOL. 134:255, 1979.)

IT HAS RECENTLY been reported that progesterone or estra-1,3,5(10)-trienen-3,17β-diol (estradiol-17β) have inhibitory effects on lymphocyte response in vitro to phytohemagglutinin (PHA)[1] or to allogeneic stimulation.[2] However, the physiologic significance of the immunosuppressive property has not yet been established, because the effective concentretions were considerably higher than those in peripheral blood during pregnancy.

We have reported an inhibitory effect of progesterone and 20α-hydroxypregn-4-en-3-one (20α-dihydroprogesterone) on lymphocyte response to PHA and have proposed that progesterone would probably suppress the maternal cell-mediated immunity at the placental site rather than at the systemic level.[3, 4] Following our previous communications, it is the purpose of the present investigation to examine whether or not the suppressive action of the steroids toward lymphocytes is reproducible in the mixed lymphocyte reactions (MLR), a recognized method of testing allograft immune reactions in vitro.

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Materials and methods

A total of 58 blood samples were taken from 40 informed healthy men and nonpregnant women who were not taking oral contraceptives. The procedure described previously[4] was followed for preparation of lymphocytes, and the lymphocyte suspension at the final concentration of 1.5×10^6 cells/ml of a mixture of tissue culture medium (RPMI-1640, Flow Laboratories, Inc., Rockville, Maryland) containing 40% (v/v) of heat-inactivated autologus plasma, 100 U/ml of penicillin G and 2.5 μg/ml of streptomycin was prepared.

Each sample of estrone, estradiol-17β, estriol, testosterone, progesterone, and 20α-dihydroprogesterone (Sigma Chemical Co., St. Louis, Missouri) was dissolved in ethanol at serial concentrations between 10^{-1} and 10^4

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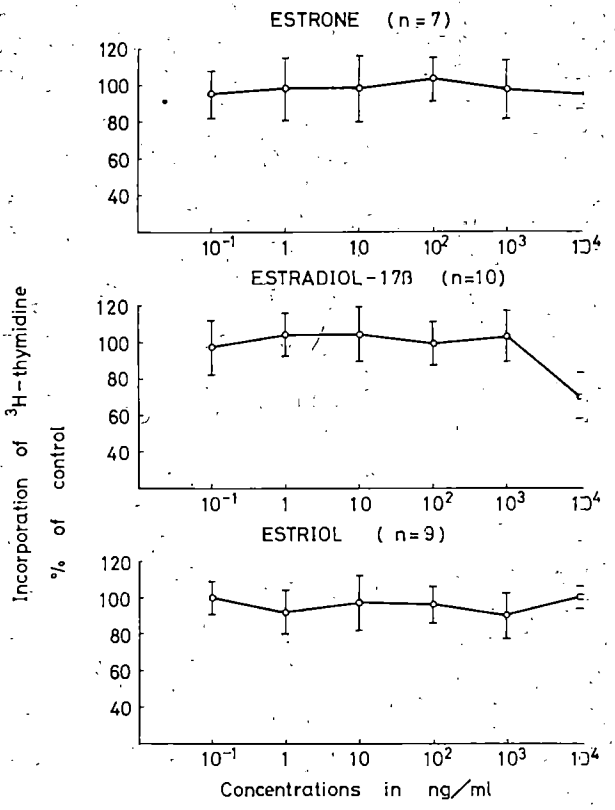


Fig. 1. Effects of estrone, estradiol-17β, and estriol on mixed lymphocyte reaction. Results expressed as mean percent incorporation of control culture ± 1 S.D.

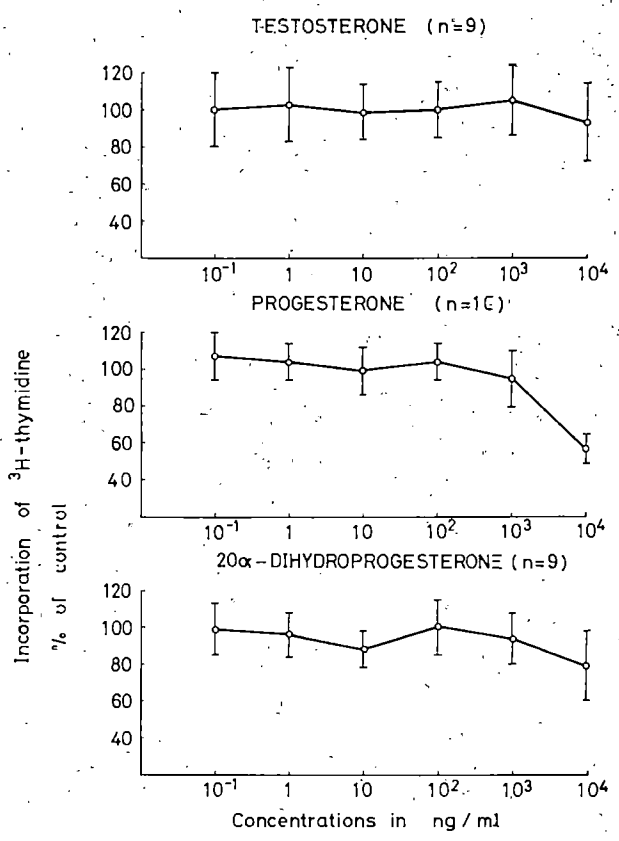


Fig. 2. Effects of testosterone, progesterone, and 20α-dihydroprogesterone on mixed lymphocyte reaction. Results expressed as mean percent incorporation of control culture ± 1 S.D.

ng/ml in 10-fold dilutions. An additional series of progesterone concentrations was prepared at 2×10^3, 4×10^3, 6×10^3, and 8×10^3 ng/ml. The effects of ethanol on incorporation of ^{3}H-thymidine into lymphocytes were checked in a preliminary experiment with a concentration range between 10^{-3} and 1% (v/v) of the culture medium. Slight suppression was observed at concentrations exceeding 0.5%, but no appreciable change in incorporation was detected at concentrations below 0.2%. Mean incorporation of ethanol control cultures was 99.8 ± 13.6% (n = 50) in the presence of 0.2% of ethanol.

Two-way MLR were prepared by the addition of 0.05 ml of each of the two sets of lymphocyte suspensions from two different individuals to each well of a flat-bottomed microtest plate (Towa Chemical Co., Tokyo) with a graduated dropper in quadruplicate. Then 0.1 ml of steroid solution was further added to each well with the final concentration of ethanol not exceeding 0.2% (v/v). Culture conditions were similar to those employed for PHA-stimulated cultures,[4] with the modifications that the first 6 day culture was followed by 18 hour culture in the presence of 0.5 μCi per well of ^{3}H-thymidine (specific activity 5.0 Ci/mmole, Radiochemical Centre, Amersham, England). Extraction of DNA and counting of the incorporated ^{3}H-thymidine were done as described previously.[4] Average counts per minute (cpm) of the quadruplicate samples were calculated and the results were expressed in terms of percentage incorporation of the control culture of the identical mixture without the addition of steroids. The results were evaluated statistically by Student's t test.

The effects of the steroids on lymphocyte viability were assessed by trypan blue dye exclusion at the end of culture under identical conditions. None of the six steroids tested showed cytotoxic activity toward lymphocytes at the concentrations tested.

Results

Effects of estrogen on the incorporation of ^{3}H-thymidine by lymphocytes. As shown in Fig. 1 and Table I, neither estrone nor estriol caused any change in incorporation of ^{3}H-thymidine into lymphocytes at the concentrations used. However, the presence of estradiol-17β at 10^4 ng/ml produced a definite reduc-

Table I. Effect of estradiol-17β on the incorporation of ^{3}H-thymidine by lymphocytes in mixed lymphocyte reactions*

Case No.	Background	MLR control	Concentrations (ng/ml) 10^{-1}	1	10	10^2	10^3	10^4
1	5	184	171	188	203	177	181	77
2	11	329	401	429	413	390	387	259
3	15	330	352	338	342	291	262	240
4	4	286	286	305	308	292	318	196
5	5	145	170	178	187	147	177	112
6	14	362	348	371	351	383	398	313
7	8	243	208	233	256	264	232	204
8	9	381	277	337	288	295	298	267
9	12	354	257	342	327	361	369	207
10	16	220	225	214	208	186	243	139
Percent incorporation Mean ± S.D.		100	96.8 ±15.8	104 ±12.1	104 ±15.0	98.5 ±11.7	103 ±14.1	70.2 ±12.6

*Figures are expressed as mean values of quadruplicate cultures in $\times 10^2$ cpm. The difference between control and the mean value at 10^4 ng/ml is statistically significant by t test ($p < 0.05$).

Table II. Effect of progesterone on the incorporation of ^{3}H-thymidine by lymphocytes in mixed lymphocyte reaction*

Case No.	Background	MLR control	Concentrations (ng/ml) 10^{-1}	1	10	10^2	10^3	2×10^3	4×10^3	6×10^3	8×10^3	10^4
1	6	394	327	299	300	314	263	275	268	184	161	137
2	8	363	375	322	302	253	270	274	276	241	219	193
3	11	249	304	275	213	232	221	194	186	142	134	125
4	23	329	—	304	279	283	230	309	225	274	250	204
5	16	155	129	123	133	114	138	127	112	112	101	79
6	16	208	196	177	193	190	148	197	136	167	132	141
7	8	185	239	213	165	195	185	138	140	141	142	132
8	14	205	—	219	195	200	246	149	134	93	104	87
9	11	232	—	227	234	221	205	171	159	172	101	92
10	6	605	—	512	543	547	488	465	531	379	293	345
11	6	203	—	231	221	186	241	164	138	140	77	114
Percent incorporation Mean ± 1 S.D.		100	102 ±17.8	95.4 ±13.5	90.2 ±8.6	88.6 ±10.0	88.0 ±17.0	79.3[a] ±7.8	71.8[b] ±6.3	66.6[a] ±12.1	56.1[c] ±12.8	53.3[d] ±10.9

*Figures are expressed as mean values of quadruplicate cultures in $\times 10^2$ cpm. Difference between control and the mean values indicated by a, b, c, and d are statistically significant by t test (a, $p < 0.025$; b, $p < 0.001$; c, $p < 0.01$; d, $p < 0.005$).

tion in ^{3}H-thymidine incorporation into lymphocytes with a statistically significant difference from the control culture.

Effects of testosterone and progestins on the incorporation of ^{3}H-thymidine by lymphocytes. The results are shown in Fig. 2. Testosterone caused no appreciable change in incorporation of ^{3}H-thymidine at the concentrations examined. An apparent reduction was observed in the presence of progesterone at 10^4 ng/ml (51.7 ± 9.6%) with a statistically significant difference from the control culture ($p < 0.001$). Although a slight decrease in incorporation was detected with 20α-dihydroprogesterone at 10^4 ng/ml (78.8 ± 18.9%), the difference from the control was not statistically significant. The suppressive effect of progesterone at concentrations differing by 2×10^3 ng/ml between 10^5 and 10^4 ng/ml are shown in Table II. The mean incorporation of ^{3}H-thymidine did not change significantly up to the concentration of 10^3 ng/ml. However, the mean incorporation began to decrease significantly at 2×10^3 ng/ml (79.3 ± 7.8%, $p < 0.025$), and diminished gradually with increasing concentrations of progesterone to reach a minimum incoropration at 10^4 ng/ml.

Comment

A dose-dependent reduction in incorporation of radioactive thymidine into lymphocytes was observed in the range of progesterone concentrations between

2×10^3 and 10^4 ng/ml, and this is in good agreement with the concentrations in which the suppressive effects of the steroid on lymphocyte response to PHA[3, 4] were detected in our previous work. It has been reported that progesterone concentration in the human placenta ranges from 2×10^3 to 6×10^3 ng/gm of tissue throughout pregnancy.[5, 6] Thus, the local concentration of progesterone displays complete agreement with the effective concentration in vitro of the steroid in the allogeneic cultures in this study as well as in the PHA-stimulated cultures.[3, 4] Therefore the present data further support the notion that progesterone probably acts as an immunosuppressant at its site of production rather than at the systemic level. This idea is strengthened by a recent elegant experiment in which rejection of hamster skin subcutaneously grafted to rats is prolonged in the presence of progesterone-contained silicone rubber capsules.[7]

Since inhibition by progesterone is apparently nonspecific, the actual role of progesterone in immunoregulation during pregnancy should be considered in view of the stages during which the suppressive effect is at work. Blocking antibodies against fetal antigens in mice[8] and the presence of specific serum factors that block maternal immune response to placental antigens[9] or to paternal antigens[10] and IgG antibodies eluted from human trophoblastic basement membranes[11] have been implicated in immunologically specific mechanisms which protect the fetus from maternal rejection. These immune controls would be mandatory for the implanted ovum to survive and a certain time period would be required for establishment of these mechanisms. There has been evidence to show the presence or active synthesis of progesterone in dividing rabbit or rodent ova at peri-implantation stages.[12, 13] Taking these data into account, together with the fact that the highest concentration of progesterone in the human placenta occurs in the earliest period after implantation, it is reasonable to assume that immunosuppression by progesterone in a nonspecific manner could be an important factor for the initial development of the embryo in utero until the specific immune mechanisms are established. If the immunologic role of progesterone is presumed for the peri-implantation stage, it is particularly intriguing that antiserum to progesterone delayed nidation and affected deleteriously the development of the embryo when it was injected into pregnant rats at the peri-implantation stage.[14]

Unexpected significant suppression was detected with estradiol-17β in this study, which did not occur in PHA-stimulated cultures. The steroid may contribute to immunoregulation during pregnancy alternatively through the induction of an immunosuppressive protein,[15] because the effective concentration in vitro is considerably higher than that in vivo in the human placenta.[16]

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Laminaria use in midtrimester abortions induced by intra-amniotic prostaglandin $F_{2\alpha}$ with urea and intravenous oxytocin

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A laminaria tent was used as an adjunct during midtrimester abortion to attempt to shorten the injection-abortion interval without adversely affecting the frequency of infection, hemorrhage, failed abortion, or cervical laceration. Eighty patients, between 14 and 20 weeks' gestation and desiring pregnancy termination, were randomized into three groups. Abortion was initiated by an intra-amniotic infusion of 20 mg of prostaglandin $F_{2\alpha}$ and 80 gm of hyperosmolar urea in Ringer's lactate (135 ml total volume), followed by oxytocin infused intravenously at 333 mU/min. Group I (N = 28) received no additional therapy; Group II (N = 23) had laminaria placed at the time of the abortifacient injection and removed 4 hours later; Group III (N = 29) had laminaria placed 4 hours prior to injection and removed at the time of injection. The injection-abortion intervals in these three groups were 17.76, 20.80, and 12.96 hours, respectively. This study illustrates that a laminaria tent placed 4 hours prior to injection is significantly more effective than a laminaria tent placed at the time of injection, and produces a shorter mean injection-abortion interval than that in patients receiving no laminaria. Furthermore, laminaria augmentation results in no demonstrable increase in the frequency of serious complications. (AM. J. OBSTET. GYNECOL. 134:260, 1979.)

MANY DIFFERENT procedures to terminate midtrimester pregnancies have been proposed. Various abortifacients, including hypertonic saline, hyperosmolar urea, prostaglandins, and prostaglandin analogues, have been used either alone or in combination and have been administered by different routes. Augmentation of these agents with intravenous oxytocin has also been employed in an attempt to shorten the treatment-abortion interval and to lower the dosage of the abortifacient(s). Unfortunately, none of these procedures for performing second-trimester abortion is ideal. As a result, searches for efficacious and safe methods continue.

The use of intracervical laminaria tents with different abortifacients has been recently investigated.[1–8] In this study we sought to determine whether use of a laminaria could shorten the time from prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$)-urea infusion to fetal passage without adversely affecting the frequency of infection, hemorrhage, failed abortion, or cervical trauma. A secondary goal was to determine which of two time schedules for laminaria insertion was preferable.

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Material and methods

Eighty women, aged 14 to 44 years, with no concurrent medical illnesses, were admitted to Brooke Army Medical Center, Fort Sam Houston, Texas, for elective midtrimester abortions. During this interval the study was carried out by a single group of investigators.

All subjects were prospectively divided by random

Table I. Clinical characteristics

	Group I	*Group II*	*Group III*
No. of patients	28	23	29
Race:			
White	23 (82)*	20 (87)	21 (73)
Black	5 (18)	3 (13)	6 (21)
Latin			1 (3)
Oriental			1 (3)
Parity:			
Nulliparas	26 (93)	14 (61)	23 (79)
Multiparas	2 (7)	9 (39)	6 (21)
Age (yr)† (mean ± S.D.)	19.1 ± 2.39	21.5 ± 5.24	20.5 ± 5.30
Gestational age (wk)† (mean ± S.D.)	17.8 ± 1.29	17.7 ± 1.52	18.1 ± 1.21

*Percent is given in parentheses.

†Means of the three groups were not statistically different.

numbers into one of three groups described below. In each patient the vagina and abdomen were carefully washed with povidone-iodine* solution. Transabdominal aminocentesis was performed aseptically with a No. 18 spinal needle after 2 cc of 1% lidocaine infiltration, and 50 cc of amniotic fluid were withdrawn. All patients were given a single intra-amniotic infusion of 20 mg of $PGF_{2\alpha}$† and 80 gm of hyperosmolar urea‡ in Ringer's lactate (135 cc total volume), followed immediately by oxytocin in 5% dextrose and 0.45% saline infused intravenously at 333 mU/min.

Group I (N = 28) received no additional therapy. In Group II (N = 23) a 5 mm in diameter, "thick" laminaria§ was placed immediately after abortifacient injection and removed 4 hours later. The laminaria was coated with sterile lubricating jelly‖ and its string was tied to a povidone-iodine–soaked vaginal pack that protruded past the introitus. In Group III (N = 29) the laminaria and vaginal pack were placed 4 hours prior to injection and removed at the time of injection.

Patients failing to pass all or parts of the placenta within 2 hours after fetal expulsion were defined as having an incomplete abortion and subjected to curettage under general anesthesia. In all subjects, after completion of the abortion, cervices were carefully inspected for potential cervical-vaginal fistulas and lacerations.

Table I characterizes the three groups of patients. Maternal age and weeks of gestation were comparable for all three groups. However, both laminaria-treated groups (II and III) had a larger percentage of multiparas than did Group I, the controls.

Three criteria were used to compare and evaluate abortifacient efficacy: (1) the proportion of subjects aborting within 24 hours of the trial period, (2) the proportion of subjects aborting within 48 hours of the trial period, and (3) the mean abortion time of those subjects aborting within the 48 hour trial period.

Four serious complications were specifically defined and studied: (1) hemorrhage (blood loss equal to or greater than 500 cc or requiring transfusion); (2) infection (two temperatures of at least 100.4° F, taken 6 hours or more apart, and associated with a tender uterus and positive cervical or blood cultures); (3) failed abortion (failure to pass the fetus within the first 48 hours after amnioinfusion); and (4) cervical trauma (a laceration or cervicovaginal fistula confirmed by postabortion inspection).

An analysis of variance was used to compare mean maternal ages and gestational lengths. The hypothesis that the mean injection-abortion intervals were the same in Groups I, II, and III was also tested by a single-factor analysis of variance. The failed abortions were not included in this analysis. After determining that these means were significantly different, pairwise comparisons of the means of the three groups were made by the Scheffé test.[9]

The cumulative abortion rate of each group was studied as a function of time from the intra-amniotic instillation of $PGF_{2\alpha}$-urea. The number of abortions occurring within 16 hour intervals was compared by means of a chi-squared contingency table. The 32 to 48 hour groups, because of small sample sizes, were pooled with the 16 to 32 hour groups for this analysis.

Results

Characterization of abortion. The mean injection-abortion intervals for patients aborting within 48 hours are given in Table II. These means for the total sam-

*Betadine, Purdue Frederick Co., Yonkers, New York.

†Prostin $F_{2\alpha}$, 5 mg/ml, The Upjohn Co., Kalamazoo, Michigan.

‡Ureaphil, Abbott Laboratories, North Chicago, Illinois.

§Dilateria, Milex Products, 5915 Northwest Hwy., Chicago, Illinois.

‖K-Y Lubricating Jelly, Johnson & Johnson, New Brunswick, New Jersey.

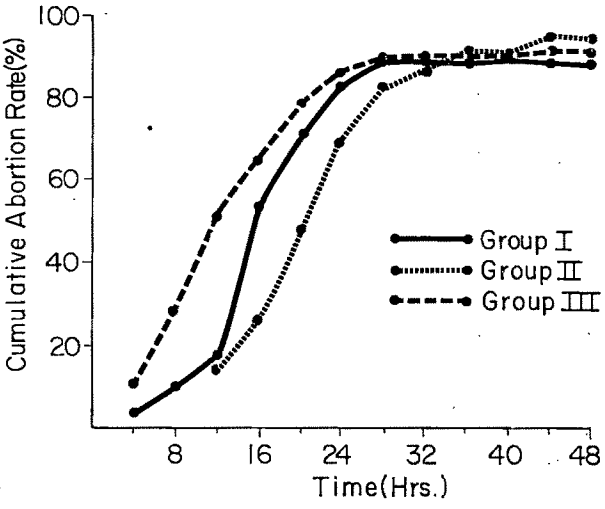


Fig. 1. The cumulative abortion rate graphed as a function of time from the intra-amniotic instillation of $PGF_{2\alpha}$-urea (in nulliparous and parous patients). Three treatment schedules are compared: $PGF_{2\alpha}$-urea alone (Group I), simultaneous laminaria $PGF_{2\alpha}$-urea (Group II), and pretreated laminaria $PGF_{2\alpha}$-urea (Group III).

ples of Groups I, II, and III were significantly different ($F_{2,\ 73} = 5.28$, $p < 0.01$). The injection-abortion interval between the two laminaria groups was significantly shorter (at an over-all significant level of $p < 0.05$) in Group III than Group II. The laminaria-pretreated patients (Group III) aborted 4.80 hours sooner (at an over-all significant level of $0.10 < p < 0.15$) than the control subjects without laminaria (Group I). The difference in mean abortion intervals between Groups I and II of 3.04 hours was not statistically different. Similar patterns existed for the mean abortion times of nulliparas and multiparas among the groups. However, group comparisons for nulliparas were not made because the F test for analysis of variance was not significant at $p < 0.05$, possibly due to reduction in sample size; group comparisons were not made for multiparas because of small sample sizes.

Fig. 1 displays the cumulative percentage of all patients who aborted over a 48 hour trial period. The number of patients in each group aborting in the first 16 hour interval versus the subsequent 32 hour interval was significantly different ($\chi^2_{(2)} = 9.19$; $p < 0.025$). This was due to the large difference between Groups II and III. The pretreatment laminaria patients (Group III) aborted more efficiently during the first 16 hours after $PGF_{2\alpha}$-urea amnioinfusion; at 24 hours after initiation of treatment a larger percentage of Group III (86.2%) had aborted than either Group I (82.1%) or Group II (69.2%). At 48 hours, however, the cumulative abortion rates of the three study groups became similar (Group I, 89.3%; Group II, 95.7%; and Group III, 93.1%).

Table II. Relationship of laminaria to injection-abortion intervals

Group	*No. of cases*	*Injection-abortion interval (hr) (mean ± S.D.)**
Nulliparas and multiparas:		
I†	27	17.76 ± 8.76
II†	22	20.80 ± 8.36
III‡	27	12.96 ± 8.55
Nulliparas:		
I†	25	17.96 ± 8.82
II	14	20.99 ± 8.87
III†	22	13.95 ± 8.70
Multiparas:		
I	2	15.38
II†	8	20.46 ± 7.97
III†	5	8.58 ± 6.25

*From intra-amniotic injection of medication to abortion of fetus.

†One failed abortion excluded.

‡Two failed abortions excluded.

Table III. Serious complications*

	Group I (28 cases)	*Group II (23 cases)*	*Group III (29 cases)*
Failed abortion	1	1	2
Hemorrhage	5	1	3
Infection	3	3	3
Cervical laceration	0	0	2

*See text for definitions.

Placental delivery. In over half (57% of Group I, 52% of Group II and 62% of Group III) of all patients the placenta was delivered within 2 hours of fetal expulsion. For those remaining subjects, the curettage rate for retained placentas of 42.5% (34/80 patients) represented the total of incomplete and failed abortions, and is similar to that usually observed for midtrimester abortion.[4]

Complications. Of all patients, 76% had uncomplicated abortions. However, among the remaining 19 patients with one or more serious complications (Table III), the frequency of these problems was not adversely affected by the addition of either simultaneous or pretreatment laminaria augmentation. The frequency of serious complications among all laminaria-treated patients (23.1%), was quite similar to our control subjects in Group I (25.0%) and compared closely with the complication rate (24.1%) of 116 patients of Duenhoelter, Gant, and Jimenez[8] treated with simultaneous laminaria and intra-amniotic $PGF_{2\alpha}$.

The incidence of serious complications (Table III) was similar among the three study groups. Among the four subjects who failed to abort the fetus within 48 hours after amnioinfusion, in only one of these patients (Group I) did the fetus not eventually pass. In this patient, the pregnancy was carefully terminated with

transvaginal use of ring clamps under general anesthesia. The most common complication was blood loss, which usually occurred during or before operative removal of the placenta. Two of these nine patients required blood transfusions. The incidence of infection in our series was closely related to the length of the infusion to fetal abortion interval. Among nine patients with febrile morbidity only one aborted in less than 16 hours. All of these patients responded well to uterine evacuation and parenteral antibiotics. Two cases of posterior vertical cervical lacerations, one 1 cm and the other 4 cm, occurred in nulliparous laminaria-pretreated patients.

Comment

The combined use of intra-amniotic $PGF_{2\alpha}$-urea is an effective method to terminate pregnancies in the midtrimester, as noted by several groups in England[10, 11] and the United States,[6, 12] and confirmed in our series. King and colleagues[13] recently showed that the minimal effective dose of $PGF_{2\alpha}$, as an augmenting agent with 80 gm of hyperosmolar urea, is not more than 5 mg. This compares with 20 mg of $PGF_{2\alpha}$ used in our study and the earlier series of King and associates.[12]

We sought to determine the effectiveness of a single laminaria tent placed only for the minimal time necessary to allow for adequate laminaria diameter expansion. A 4 hour period of laminaria insertion was believed appropriate because Hale and Pion[14] showed that close to maximal laminaria diameter swelling occurred within 4.6 hours of insertion; even an additional 15.7 hours of insertion time achieved only 1.2 mm further enlargement in diameter.

The greatest difference in the mean injection-abortion interval among the three groups is between the two laminaria groups. However, laminaria insertion at the time of abortifacient injection (Group II) did not significantly shorten the injection-abortion interval. This result supports the findings of other studies.[4, 6] Perhaps laminaria are ineffective when inserted concurrent with abortifacient initiation because (1) cervical dilation from the abortifacients may have been greater than the rate of intrinsic laminaria expansion and (2) a "plug effect" by the laminaria and its vaginal pack may have mechanically impeded fetal abortion.

By contrast, laminaria tents inserted 4 hours prior to abortifacient injection shortened the injection-abortion interval. Recent studies by Stubblefield and associates,[2] using intra-amniotic $PGF_{2\alpha}$, and Bieniarz and associates,[3] using an intramuscularly administered prostaglandin analogue, also showed that laminaria pretreatment makes termination of pregnancy a more rapid event. These investigators used as many as four laminaria, which were left in the cervix overnight for 12 to 18 hours prior to prostaglandin use.[3, 5] Their increased number of laminaria tents may have contributed to shorter abortion intervals than ours. In the series of Stubblefield and associates[5] of 230 pretreatment patients, the mean injection-abortion interval was shorter with two laminaria compared to one laminaria, and improved further when three laminaria were employed. It is less likely that the longer length of pretreatment used by Stubblefield and associates[5] had a beneficial effect because the mean injection-abortion interval for single laminaria use in pretreated patients showed no improvement over our results with only 4 hours' pretreatment.

Our total complication rate of 23.8% cannot be ignored. Perhaps combining intramuscular administration of a prostaglandin analogue with laminaria pretreatment[3] will not only be as rapid as but also safer than our method. In our series retained placenta, hemorrhage, and infection were problems which had similar frequency in both control and laminaria-augmented subjects. As noted independently by both Stubblefield and associates[5] and Lischke and Gordon,[15] and confirmed in our series, cervical rupture, a complication of midtrimester abortion,[16] can still occur despite use of laminaria. Therefore, we examine cervices after all midtrimester abortions, including those utilizing laminaria.

Laminaria tents may potentially cause other serious problems. These include migration toward the uterine fundus if collar devices are not used,[17] incarceration of the laminaria in the cervical canal,[18] and even laminaria fragmentation with loss of the fragments in the uterine cavity.[18] We failed to observe such complications.

In conclusion, a single laminaria tent placed 4 hours prior to $PGF_{2\alpha}$-urea injection produced the shortest injection-abortion interval when compared to (1) laminaria placed at the time of injection and (2) no laminaria treatment. This decrease in the abortion time is not accompanied by a demonstrable increase in the frequency of serious complications.

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Discussion

DR. JOSEPH BIENIARZ, Chicago, Illinois. The development of a safe, simple, and efficient method of midtrimester pregnancy termination forms a continuous challenge to fertility control. Dr. Strauss has made an effort to limit the complications and to shorten the induction-abortion time (IAT) by laminaria insertion in patients treated with intra-amniotic instillation of Prostin PGF_2 and urea, combined with intravenous infusion of syntocinon. He used a prospective randomized design to assess the significance of the differences between the mean IAT in the two study groups—(1) one with laminaria inserted at the onset of treatment and (2) the other inserted 4 hours earlier—and (3) a control group treated without laminaria insertion.

With three pairs of means to be compared the authors were forced to use the controversial least significant difference after the analysis of variance, instead of the simple t test. Such repeated comparisons are not independent; therefore, the probability values associated with these statistics do not have the conventionally accepted meaning. The investigator is left with the impression that he has more information than is truly available. It can be shown that with three treatments, the observed value of t for the greatest difference will exceed the tabulated 5% level about 13% of the time; with six treatments the figure is 40%. Thus, when the investigator thinks he is making a t test at the 5% level, he is actually testing at the 13% level for three treatments.*

The three groups were well matched with respect to maternal and gestational age (Table I). They were not matched as to parity (Table III), which is an important omission. While the control Group I, with a long 18 hour IAT, consists almost exclusively of nulliparas, the laminaria-pretreated Group III had a short 9 hour IAT, known to be related to multiparity.

A simple laminaria tent inserted at the onset of induction did not increase the efficiency of treatment. A single laminaria tent inserted 4 hours earlier and withdrawn when treatment was started shortened the IAT significantly, and did not increase the rate of complications. In our experience three to four laminarias inserted snugly into the cervix act better than a single one, if they remain longer—at least 12 hours. Laminaria act slowly and gradually dilate the cervix. Their main advantage consists in protecting the cervix from trauma and disruption caused by forceful rapid dilatation or by intravenous infusion of a potent oxytocic. In this way, cervical incompetency can be avoided.

*Since this original discussion by Dr. Bieniarz, the authors have revised their statistical method and have substituted the more conservative Scheffé test for the least significant difference after the analysis of variance.

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Mead Johnson Pharmaceutical Division
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NEW DURICEF®
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A new oral cephalosporin for urinary tract infections due to *Escherichia coli, Proteus mirabilis,* and *Klebsiella* sp. distinguished by sustained, higher urine levels

Numerous human pharmacological studies have now clearly established that the outstanding metabolic characteristic of cefadroxil, which differentiates it from other presently marketed cephalosporins such as cephalexin and cephradine, is its prolonged duration of action."[1]

"...for cephalosporins, a longer half-life might be more useful than higher peak levels."[2]

For complete prescribing information, see last page of this advertisement.



For treatment of urinary tract infections due to *Escherichia coli*, *Proteus mirabilis*, and *Klebsiella* sp.

NEW DURICEF®
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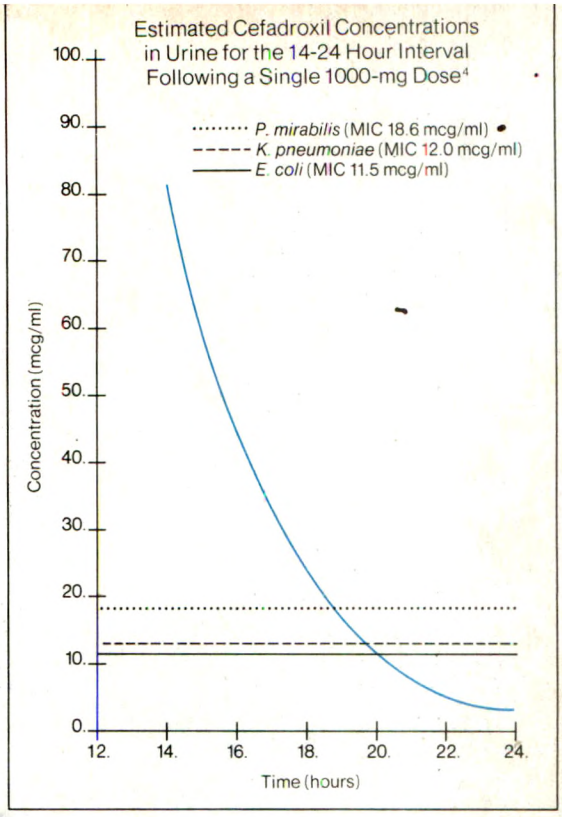
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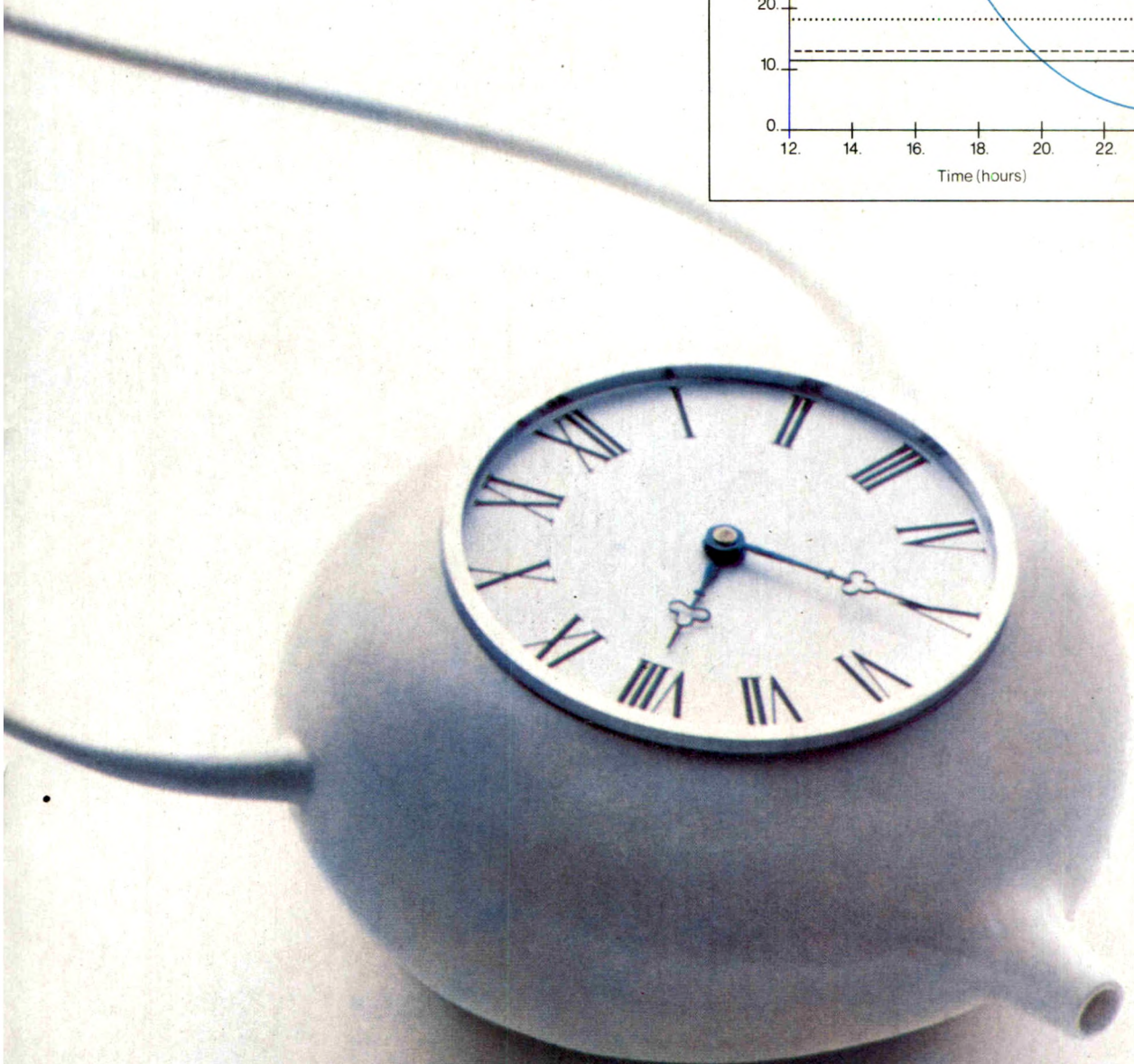
PROLONGED DURATION OF ACTION

"Numerous studies have shown that effective antimicrobial activity in urine is most important in curing urinary tract infections.... a continuous urinary antibiotic concentration above the MIC of the infecting organism can cure the majority of urinary tract infections, whether of renal or bladder origin."[3]

SUSTAINED HIGHER URINE LEVELS

- Cefadroxil concentration in urine is maintained well above the MICs for all typical urinary pathogens for 12 hours and, in most instances, for 18 hours.[3]
- After single equivalent doses, the antibiotic concentration in urine is three times higher for cefadroxil at 6 to 12 hours than for cephalexin[3]
- The prolonged duration of action is due to a more gradual urinary excretion rate compared to cephalexin and cephradine.[1,3]
- Twenty-four hours after ingestion, approximately 93% of cefadroxil is recovered in the urine.[3]





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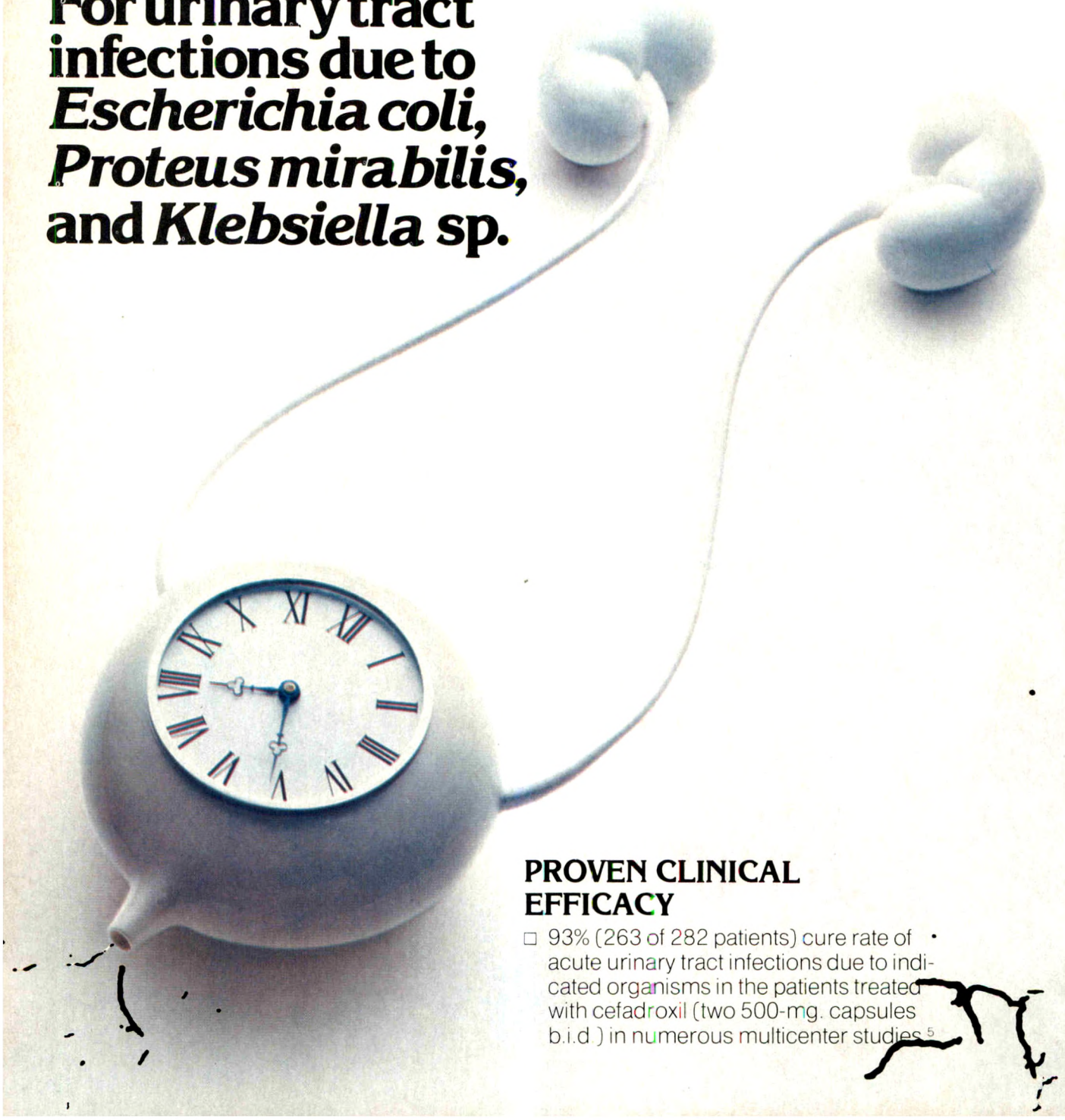
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For urinary tract infections due to *Escherichia coli*, *Proteus mirabilis*, and *Klebsiella* sp.



PROVEN CLINICAL EFFICACY

- 93% (263 of 282 patients) cure rate of acute urinary tract infections due to indicated organisms in the patients treated with cefadroxil (two 500-mg. capsules b.i.d.) in numerous multicenter studies.[5]

IIGH DEGREE)F SAFETY

Laboratory parameters in more than 175 studies in 15 countries have failed to reveal any drug-related changes regarded as clinically significant.[4]

In none of these studies was there any tendency for cefadroxil to accumulate in the serum nor has nephrotoxicity been reported.[4]

DURICEF can be used in patients with renal insufficiency at reduced dosages (see full prescribing information).

There is evidence of partial cross-allergenicity between the penicillins and the cephalosporins.

The most frequent adverse reaction has been nausea...rarely severe enough to warrant cessation of therapy. Administration with food decreases the chances of nausea occurring and does not affect absorption.

References: 1. Henness DM, Richards D, Santella PJ, Rubinfeld J: Oral bioavailability of cefadroxil, a new semisynthetic cephalosporin. *Clin Therap* 1:263-273, 1977. **2.** Grasso S, Meinardi G, DeCarneri I, Tamassi V: New in vitro model to study the effect of antibiotic concentration and rate of elimination on antibacterial activity. *Antimicrob Agents Chemother* 13:570-576, 1978. **3.** Hartstein AI, Patrick KE, Jones SR, et al: Comparison of pharmacological and antimicrobial properties of cefadroxil and cephalexin. *Antimicrob Agents Chemother* 12:93-97, 1977. **4.** Data on file, Mead Johnson Pharmaceutical Division. **5.** Henness DM, Richards D: Clinical comparison of cefadroxil and cephalexin in uncomplicated urinary tract infection. *Curr Ther Res* 23:547-554, 1978.

B.I.D. CONVENIENCE AND COMPATIBILITY WITH FOOD

B.I.D. CONVENIENCE

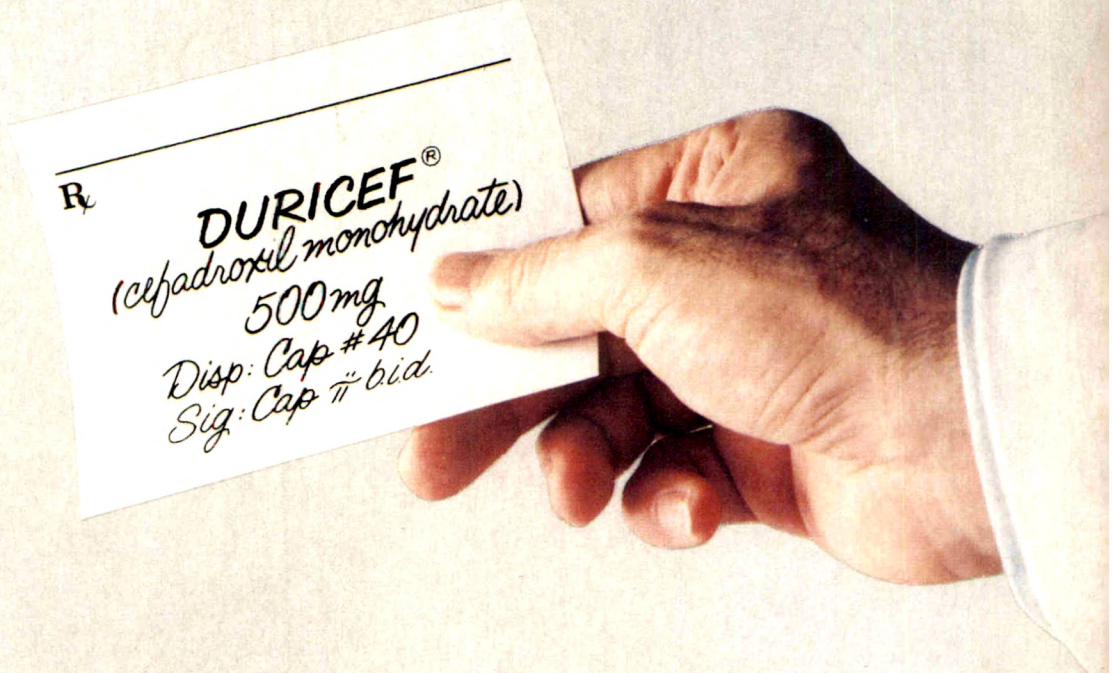
Sustained high urine levels in comparison with other oral cephalosporins justify a simple two-capsule b.i.d. regimen in urinary tract infections.

COMPATIBILITY WITH FOOD

Concomitant administration of DURICEF with food does not affect its rate or extent of absorption. This may be helpful in diminishing potential gastrointestinal complaints occasionally associated with oral cephalosporin therapy.

ENHANCED DOSAGE COMPLIANCE

The convenient regimen of DURICEF—two capsules b.i.d., at breakfast and dinner—improves the chances for patient compliance and increases the likelihood of patients completing therapy as prescribed.



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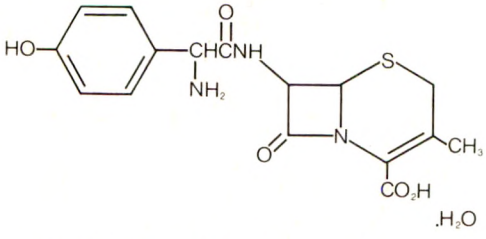
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DURICEF®
(CEFADROXIL MONOHYDRATE)



A new oral cephalosporin offering tangible clinical benefits... plus b.i.d. convenience

DESCRIPTION: DURICEF® (cefadroxil monohydrate) is a semisynthetic cephalosporin antibiotic intended for oral administration. It is a white to yellowish-white crystalline powder. It is soluble in water and it is acid-stable. It is chemically designated as 7-[[D-2-amino-2-(4-hydroxyphenyl)acetyl]amino]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid monohydrate. It has the following structural formula:



Clinical Pharmacology—DURICEF (cefadroxil monohydrate) is rapidly absorbed after oral administration. Following single doses of 500 and 1000 mg., average peak serum concentrations were approximately 16 and 28 mcg./ml., respectively. Measurable levels were present 12 hours after administration. Over 90 percent of the drug is excreted unchanged in the urine within eight hours. Peak urine concentrations are approximately 1800 mcg./ml. during the period following a single 500 mg. oral dose. Increases in dosage generally produce a proportionate increase in DURICEF urinary concentration. The urine antibiotic concentration was maintained well above the MIC of all typical urinary pathogens for 12 hours and, in most instances, for 18 hours.

MICROBIOLOGY: *In vitro* tests demonstrate that the cephalosporins are bactericidal because of their inhibition of cell-wall synthesis. DURICEF is active against the following organisms *in vitro*:

Escherichia coli — *Klebsiella species*
Proteus mirabilis

Note—Most strains of *Enterococci (Streptococcus faecalis* and *S. faecium)* are resistant to DURICEF. It is not active against most strains of *Enterobacter species, P. morganii,* and *P. vulgaris.* It has no activity against *Pseudomonas* or *Herella species.*

Disc Susceptibility Tests—Quantitative methods that require measurement of zone diameters give the most precise estimates of antibiotic susceptibility. One recommended procedure (CFR Section 460.1) uses cephalosporin class disc for testing susceptibility; interpretations correlate zone diameters of this disc test with MIC values for DURICEF. With this procedure, a report from the laboratory of "resistant" indicates that the infecting organism is not likely to respond to therapy. A report of "intermediate susceptibility" suggests that the organism would be susceptible if the infection is confined to the urinary tract, as DURICEF produces high antibiotic levels in the urine.

INDICATIONS: DURICEF (cefadroxil monohydrate) is indicated for the treatment of urinary tract infections caused by *E. coli, P. mirabilis,* and *Klebsiella species.*

Note—Culture and susceptibility tests should be initiated prior to and during therapy. Renal function studies should be performed when indicated.

CONTRAINDICATION: DURICEF (cefadroxil monohydrate) is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNING: IN PENICILLIN-ALLERGIC PATIENTS, CEPHALOSPORIN ANTIBIOTICS SHOULD BE USED WITH GREAT CAUTION. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES OF PATIENTS WHO HAVE HAD REACTIONS TO BOTH DRUGS (INCLUDING FATAL ANAPHYLAXIS AFTER PARENTERAL USE).

Any patient who has demonstrated a history of some form of allergy, particularly to drugs, should receive antibiotics cautiously and then only when absolutely necessary. No exception should be made with regard to DURICEF (cefadroxil monohydrate).

PRECAUTIONS: Patients should be followed carefully so that any side-effects or unusual manifestations of drug idiosyncrasy may be detected. If a hypersensitivity reaction occurs, the drug should be discontinued and the patient treated with the usual agents (e.g., epinephrine or other pressor amines, antihistamines or corticosteroids).

DURICEF (cefadroxil monohydrate) should be used with caution in the presence of markedly impaired renal function (creatinine clearance rate of less than 50 ml/min/1.73 M^2). (See Dosage and Administration.) In patients with known or suspected renal impairment, careful clinical observation and appropriate laboratory studies should be made prior to and during therapy.

Prolonged use of DURICEF may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Positive direct Coombs tests have been reported during treatment with the cephalosporin antibiotics. In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs test may be due to the drug.

USAGE IN PREGNANCY: Although no teratogenic or anti-fertility effects were seen in reproductive studies in mice and rats receiving dosages greater than the normal human dose, the safety of this drug for use in human pregnancy has not been established. The benefits of the drug in pregnant women should be weighed against a possible risk to the fetus.

ADVERSE REACTIONS: Gastrointestinal—The most frequent side-effect has been nausea. It was infrequently severe enough to warrant cessation of therapy. Administration with food decreases nausea and does not decrease absorption. Diarrhea and dysuria have also occurred.

Hypersensitivity—Allergies (in the form of rash, urticaria, and angioedema) have been observed. These reactions usually subsided upon discontinuation of the drug.

Other reactions have included genital pruritus, genital moniliasis, vaginitis, and moderate transient neutropenia.

DOSAGE AND ADMINISTRATION: DURICEF (cefadroxil monohydrate) is acid stable and may be administered orally without regard to meals. Administration with food may be helpful in diminishing potential gastrointestinal complaints occasionally associated with oral cephalosporin therapy.

Adults—The usual adult dose is one g. (two 500 mg. capsules) two times per day for patients with normal renal function. In patients with renal impairment, the dosage of cefadroxil should be adjusted according to creatinine clearance rates to prevent drug accumulation. The following schedule is suggested. In adults, the initial dose is 1000 mg. of DURICEF (cefadroxil monohydrate) and the maintenance dose (based on the creatinine clearance rate [ml/min/1.73M^2]) is 500 mg. at the time intervals listed below.

Creatinine Clearances	Dosage Interval
0-10 ml/min	36 hours
10-25 ml/min	24 hours
25-50 ml/min	12 hours

Patients with creatinine clearance rates over 50 ml/min may be treated as if they were patients having normal renal function.

Children—Dosage and safety have not yet been established in children.

HOW SUPPLIED: DURICEF® (cefadroxil monohydrate) capsules 500 mg. for oral administration in an opaque maroon cap and opaque white body No. 0 hard gelatin capsule. On each half capsule printed in black is "MJ" and "500." Available in bottles of 24 capsules (NDC 0087-0784-41) and 100 capsules (NDC 0087-0784-42).

U.S. Patent Re—29,16

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FETUS, PLACENTA, AND NEWBORN

13,14-Dihydro-15-keto-prostaglandin $F_{2\alpha}$ concentrations in human plasma and amniotic fluid

R. B. GHODGAONKAR, B.PHARM.
N. H. DUBIN, PH.D.
D. A. BLAKE, PH.D.
T. M. KING, M.D., PH.D.
Baltimore, Maryland

An antiserum to 13,14-dihydro-15-keto-prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}M$) was prepared and a radioimmunoassay evaluated in various reproductive states. $PGF_{2\alpha}M$ plasma concentration was 63.6 ± 10.3 pg/ml (mean ± SEM) in cycling women. The concentration fluctuated throughout the menstrual cycle and pregnancy, but no discernible patterns were noted. $PGF_{2\alpha}M$ concentrations were elevated at the time of urea + oxytocin induced abortion (238 ± 54 pg/ml) and during late stages of normal labor (352 ± 107 pg/ml) but were not elevated during labor prior to 7 cm dilatation. Following intra-amniotic instillation of 5 mg of $PGF_{2\alpha}$ tromethamine into the amniotic sac, $PGF_{2\alpha}M$ concentration increased in the amniotic fluid. In the plasma of these patients there was an eighteenfold rise in plasma $PGF_{2\alpha}M$ concentration compared to a 3.5-fold rise in $PGF_{2\alpha}$ at 1 hour, suggesting changes in $PGF_{2\alpha}M$ may be more easily detected than the parent compound. While $PGF_{2\alpha}M$ may be a useful index of $PGF_{2\alpha}$ production, it appears that $PGF_{2\alpha}M$ is of little value in predicting the occurrence of uterine contraction. (AM. J. OBSTET. GYNECOL. 134:265, 1979.)

CIRCULATING physiologically active prostaglandins have a short half life due to rapid metabolism by the lungs, liver, and other organs.[1] There is also evidence that prostaglandins are metabolized to inactive forms within the cells of origin prior to secretion.[2, 3] It has been suggested, therefore, that measuring the metabolite rather than the parent compound might better reflect changes in production of prostaglandins.[4] The major circulating metabolite of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) is 13,14-dihydro-15-keto-prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}M$). This paper describes $PGF_{2\alpha}M$ plasma concentrations in various reproductive states and compares amniotic fluid (AF) and plasma $PGF_{2\alpha}$ with $PGF_{2\alpha}M$ during midtrimester abortions induced with intra-amniotic hyperosmolar urea and $PGF_{2\alpha}$.

From the Department of Gynecology and Obstetrics, The Johns Hopkins Hospital.

These studies were carried out under Contract AID/csd-3627.

Received for publication March 20, 1978.

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Accepted July 19, 1978.

Reprint requests: Dr. T. M. King, Department of Gynecology and Obstetrics, The Johns Hopkins University, School of Medicine, Baltimore, Maryland 21205.

Material and methods

Antiserum preparation. Antiserum was prepared by coupling $PGF_{2\alpha}M$ to bovine serum albumin (BSA) by the carbodiimide method and rabbits were immunized as previously described.[5] An average of 29 molecules of $PGF_{2\alpha}M$ were coupled to each molecule of BSA as determined by retention of $PGF_{2\alpha}M$ trace following dialysis. Blood, obtained by cardiac puncture, contained a peak titer at 1 month, and the titer remained

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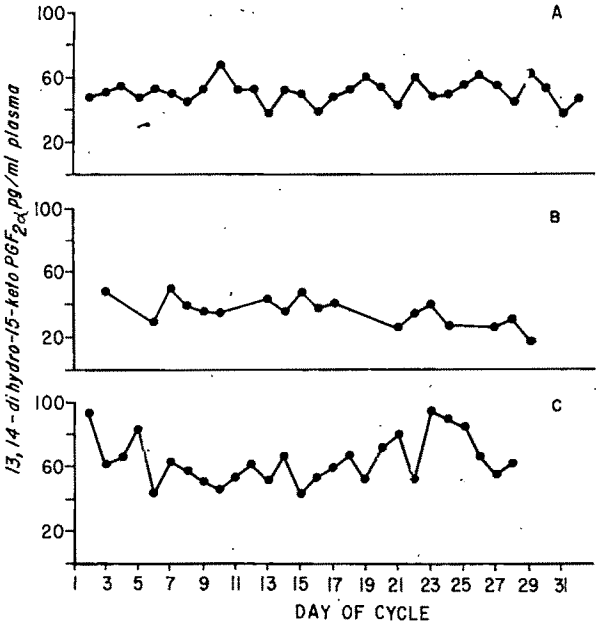


Fig. 1. Plasma $PGF_{2\alpha}M$ concentrations in three normal women observed serially throughout the menstrual cycle. Day 1 s the first day of menstrual bleeding.

high for 10 months at which time the rabbit was killed and blood collected.

Radiommunoassay. A standard curve was prepared in tricine-buffered saline (TBS) containing gelatin (1 mg/ml) for the range of 0 to 320.0 pg of $PGF_{2\alpha}M$. Antiserum was diluted with TBS (1:20,000) and 0.1 ml of this dilution was added to a tube containing 0.1 ml unextracted plasma, 0.1 ml standard, or 0.1 ml TBS (zero tube) and was incubated for 30 minutes at room temperature. The radioisotope [5,6,8,11,12,14(n)-^{3}H]13,14-dihydro-15-keto-$PGF_{2\alpha}$ (specific activity 85 Ci/mmole) was obtained from Amersham Searle Corporation, Chicago, Illinois. A stock solution containing 10 μCi/ml in ethanol: water (7:3) was stored at −20° C. On the day of assay, 25 μl was removed, dried under nitrogen, and redissolved in 10.6 ml of TBS. 0.1 ml volume (approximately 2,500 cpm with a mass of 10 pg) was added to each tube and incubated overnight at 4° C.

The next day the antibody-bound complex was precipitated by addition of 1.0 ml of 68% saturated ammonium sulfate suspension containing 4% calcium sulfate as described previously.[6] The contents were mixed and allowed to stand at 4° C for 10 minutes. The tubes were centrifuged for 30 minutes at 2,000 rpm at 4° C. Then 0.8 ml of supernatant (free phase) was added to 10 ml of toluene-based scintillation cocktail and counted for 10 minutes. The corresponding values were read from the standard curve and expressed in terms of $PGF_{2\alpha}M$ concentration in picograms per milliliter of sample.

The minimum mass of $PGF_{2\alpha}M$ necessary to cause a displacement of ^{3}H-$PGF_{2\alpha}M$ from the antibody, which was significantly different from the zero tube, was 1.25 pg and the working range extended to 100 pg. "Charcoal-stripped" plasma gave blank values that averaged 2.1 pg/0.1 ml. The correlation coefficient between added and observed mass of $PGF_{2\alpha}M$ was 0.99 and the slope of the regression line was 0.89 with the Y intercept close to zero. The within-assay coefficient of variation was 5% and the between-assay coefficient of variation was 16%. The cross-reaction of related prostaglandins was tested for their ability to displace ^{3}H-$PGF_{2\alpha}M$ from the antibody relative to $PGF_{2\alpha}M$. The results found are as follows: 13,14-dihydro-$PGF_{2\alpha}$, 3%; 15-keto-$PGF_{2\alpha}$, 0.01%; 13,14-dihydro-15-keto-PGE_2, 1%; 15-keto-PGE_2, <0.01%.

$PGF_{2\alpha}$ was measured by the method of Salmon and Amy.[7] The antiserum was provided by Dr. S. M. M. Karim, Singapore. The antibody shows some cross-reaction with other prostaglandins of the F series, but cross-reaction with the E series is less than 1%. Interassay coefficient of variation was 15% and intra-assay coefficient of variation was 9%.

Clinical studies. One blood sample was obtained from each patient and plasma $PGF_{2\alpha}M$ was determined and compared in the following groups of women: (1) those in the follicular stage of the menstrual cycle; (2) those using a combined oral contraceptive (5 mg norgestrel and 50 μg ethinyl estradiol); (3) those with uncomplicated pregnancies, 17 to 20 weeks after the last menstrual cycle (this group was further separated into those at less than and those at greater than 7 cm dilatation; (4) elective abortion parients, 17 to 20 weeks pregnant, at the time of abortion (these patients were injected with intra-amniotic hyperosmolar urea (80 gm) followed by intravenous oxytocin (332 mU/min.).

The following patients had multiple blood samples drawn. Daily plasma samples from three women throughout the menstrual cycle and sequential samples from two pregnant women were also assayed. Eight multiparous patients over 18 years of age seeking termination of a midtrimester pregnancy, and who gave informed consent, participated in the following study. An 18 gauge butterfly needle was placed in the right antecubital vein for collection of blood samples prior to and at timed intervals (t = 0, 0.25, 1, 4, 8, and 12 hours) following abortifacient injection. Polyethylene tubing was inserted into the amniotic cavity through which AF was withdrawn and replaced by 134 ml of 5% dextrose containing 80 gm urea and 5 mg $PGF_{2\alpha}$

tromethamine. This initiation of the injection was considered time zero (t = 0). This procedure is discussed in detail in another publication.[8] The tubing was left in place so that AF could be sampled at intervals corresponding to the blood sampling prior to rupture of membranes. Urea added to prostaglandin standards was found not to affect the radioimmunoassay displacement curves.

All blood samples were collected and stored on ice in heparinized tubes containing indomethacin (5 ug/ml blood) and the plasma was immediately separated by centrifugation and frozen until assayed. All samples were assayed in duplicate.

Results

Plasma $PGF_{2\alpha}M$ concentrations for women in various reproductive states are listed in Table I. Levels of $PGF_{2\alpha}M$ at the time of induced abortion were significantly higher than pregnant women not in labor at the same stage of pregnancy (65.5 ± 8.6 SEM vs. 238.3 ± 54.5 pg/ml). There was no detectable increase in $PGF_{2\alpha}M$ in early labor (< 7 cm), however, there was a significant increase at 8 cm to 1 hour post partum (Table I). Although $PGF_{2\alpha}M$ values fluctuated throughout the cycle, there appeared to be no discernible pattern (Fig. 1). Values fluctuated in individual patients throughout pregnancy, but again there appeared to be no pattern (Fig. 2).

Following $PGF_{2\alpha}$ instillation into the amniotic sac, the AF concentration of $PGF_{2\alpha}$ increased from 0.15 ± 0.01 to 6,250 ± 1,300 ng/ml in 15 minutes. After 1 hour, there was a decline in $PGF_{2\alpha}$ concentration which reached 1,370 ± 970 ng/ml by 12 hours. The disappearance half life (time for concentration to fall to 50% of the back-extrapolated time zero concentration) was 4.5 hours (Fig. 3). The apparent volume of distribution of PGF was calculated by dividing the injected dose of $PGF_{2\alpha}$ (5 mg) by the extrapolated concentration of $PGF_{2\alpha}$ at time zero (7,000 ± 1,500 ng/ml) and found to be 710 ± 150 ml. $PGF_{2\alpha}M$ increased in AF within 15 minutes of injection from 0.24 ± 0.05 to 53.7 ± 24.8 ng/ml. These levels continued to rise until 8 hours when the concentration reached 377 ± 103 ng/ml.

In the plasma, $PGF_{2\alpha}$ concentration increased by 1 hour after intra-amniotic administration of $PGF_{2\alpha}$ from 0.32 ± 0.03 to 1.09 ± 0.27 ng/ml. There was no significant change in these levels over the next 12 hours. $PGF_{2\alpha}M$ increased from 0.07 ± 0.01 to 0.76 ± 0.31 ng/ml plasma in 15 minutes and remained above the preinjection values for 12 hours. The average concentration in $PGF_{2\alpha}M$ in plasma increased eightfold at 1 hour after amniotic injection of

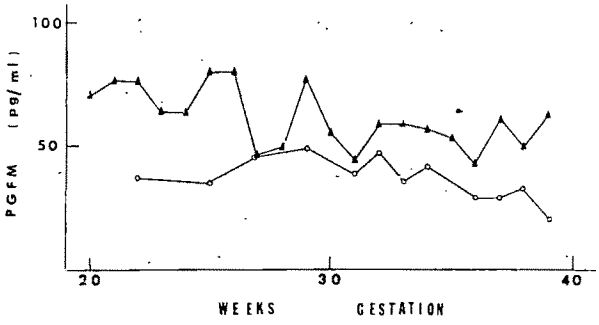


Fig. 2. Plasma $PGF_{2\alpha}M$ concentrations in two women followed serially during pregnancy.

Table I. Concentration of $PGF_{2\alpha}M$ in plasma from women

Classification	*No.*	*$PGF_{2\alpha}M$ (pg/ml)*
Cycling (follicular stage)	6	64 ± 10*
Oral contraceptives	7	62 ± 7
Pregnant (17-20 wk.)	10	66 ± 9
Abortion (17-20 wk.)	8	238 ± 54†
Labor (<7 cm)	8	47 ± 6
Labor (>7 cm to 1 hr. post partum)	6	352 ± 107†

*Standard error of the mean.

†Significantly greater (P < 0.01) than all values without dagger (by F test following analysis of variance).

$PGF_{2\alpha}$ compared to a 3.5-fold rise in average $PGF_{2\alpha}$ concentration (Fig. 4).

Comment

Changes in the pattern of plasma $PGF_{2\alpha}$ have not been shown during the menstrual cycle[9] despite the fact that increased levels have been shown in endometrial tissue[10] and jet washes of endometrium[11] during the luteal phase. In the present study, while there was a day-to-day variation in plasma $PGF_{2\alpha}M$, no obvious pattern in plasma $PGF_{2\alpha}M$ was apparent during the menstrual cycle of any of the three subjects studied. No difference was seen between women using combined oral contraceptives and control women in the follicular stage of their cycle (61 ± 7.4 vs. 63.6 ± 10.3 pg/ml).

Following intra-amniotic administration of 5 mg $PGF_{2\alpha}$, the AF disappearance rate of $PGF_{2\alpha}$ was found to be 4.5 hours. The volume of distribution was 710 ± 150 ml. This volume agrees well with that found for urea in the same patients.[8] These results suggest that the $PGF_{2\alpha}$ was distributed to an apparent space larger than AF, the volume of which was estimated to be about 200 to 300 ml based on the amount removed at the time of injection. The other compartments to which the $PGF_{2\alpha}$ is most likely distributed includes the

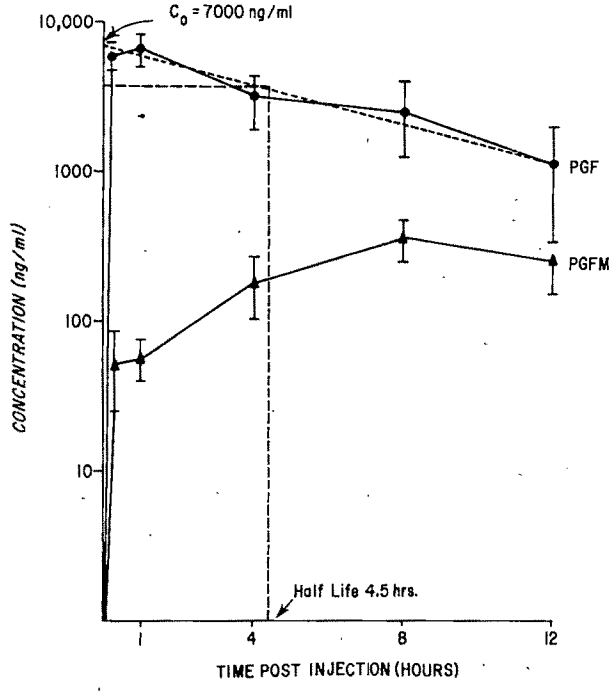


Fig. 3. Concentration of $PGF_{2\alpha}$ and $PGF_{2\alpha}M$ in AF following intra-amniotic $PGF_{2\alpha}$ (5 mg) administration. $PGF_{2\alpha}$ was administered along with 80 gm urea to induce abortion. Dotted line through $PGF_{2\alpha}$ curve represents the regression line (fitted to an exponential decay curve) for $PGF_{2\alpha}$ extrapolated to time 0 to estimate the concentration at time 0 (C_0). Number of patients = 8. Vertical line indicates standard error of the mean.

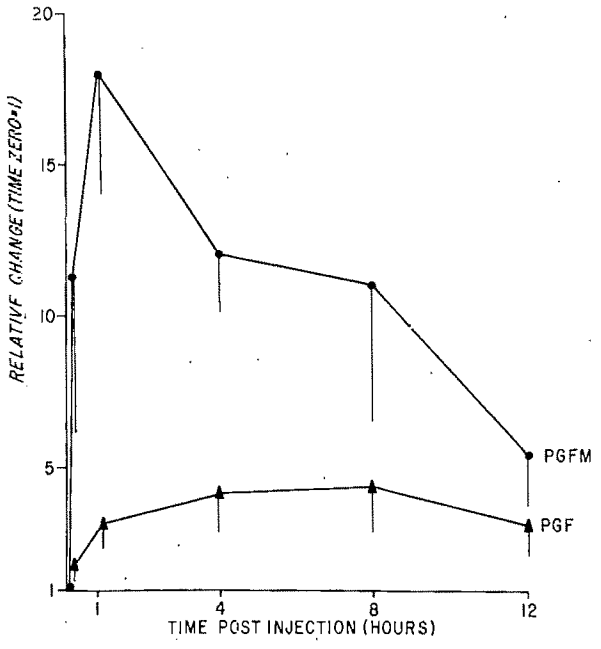


Fig. 4. Relative change in plasma $PGF_{2\alpha}$ and $PGF_{2\alpha}M$ following intra-amniotic administration of 5 mg $PGF_{2\alpha}$. Time 0 relative change was defined as 1. $PGF_{2\alpha}$ was administered along with 80 gm urea to induce abortion. Number of patients = 8. Vertical line indicates standard error of the mean.

fetus and placenta as demonstrated pharmacokinetically for urea in rhesus monkeys.[12]

Following intra-amniotic injection of $PGF_{2\alpha}$ AF $PGF_{2\alpha}M$ concentration increased gradually with time, indicating some metabolism occurring in the fetal compartment and/or maternal conversion and transfer back to the fetus. The relative change in $PGF_{2\alpha}M$ at 1 hour after injection was greater (peak = 18 × initial value) compared to $PGF_{2\alpha}$ (3.5 × initial value), suggesting changes in $PGF_{2\alpha}M$ may be more easily detected than $PGF_{2\alpha}$. The patterns of $PGF_{2\alpha}$ and $PGF_{2\alpha}M$ concentration with time are similar to those in three patients reported previously by Cornett, Harrison, and Kirton[3] despite the fact that a 40 mg dose of $PGF_{2\alpha}$ without urea was injected intra-amniotically compared to our 5 mg dose. That study also differed in that the initial $PGF_{2\alpha}M$ levels were about tenfold greater than in this report which may be related to the specificity and sensitivity of the antibody. Plasma levels of $PGF_{2\alpha}M$ reported in the literature range from 38[4] to 1,400 pg/ml[3] as measured by radioimmunoassays. Our values are in the lower range and agree in magnitude with values obtained by the tedious but more precise method of gas chromatography–mass spectrophotometry.[13]

$PGF_{2\alpha}$ is a potent oxytocic agent which is endogenously produced in increasing amounts by actively contracting uteri.[14, 15] Since circulating $PGF_{2\alpha}$ is rapidly metabolized by prostaglandin dehydrogenase and Δ^{13} reductase,[1] it has been suggested that $PGF_{2\alpha}M$ may more accurately reflect changes in production of $PGF_{2\alpha}$.[4] Also, in vitro $PGF_{2\alpha}$ production has been documented after blood is collected[16] whereas this seems not to be the case for $PGF_{2\alpha}M$ yielding an additional advantage of $PGF_{2\alpha}M$ measurements.

In this study, a 3.6-fold increase in plasma $PGF_{2\alpha}M$ levels was found in induced abortion patients at the time of high uterine activity as compared to controls of the same gestational age not in labor. In early labor, there was no detectable rise in plasma $PGF_{2\alpha}M$ until after 7 cm dilatation, at which time levels were significantly increased. While $PGF_{2\alpha}M$ may be a good index of $PGF_{2\alpha}$ production, it appears that $PGF_{2\alpha}M$ is of little value in predicting the occurrence of uterine contractions.

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Reduced uterine blood flow and fetal hypoxemia with acute maternal stress: Experimental observation in the pregnant baboon

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The effects of maternal hyperexcitability on the fetus were studied in 17 baboons. In the period of agitation, induced by stressful stimulus such as exposure to bright light or by clamping of the toe, the mother exhibited an increase in arterial blood pressure and, in some instances, arrhythmia. These changes were accompanied by an increased uterine activity and reduced uterine blood flow, and resulted in a decrease in heart rate and arterial oxygenation in all fetuses. Fetal recovery was prompt after maternal agitation was terminated, either by removal of the stimulus or by sedation with pentobarbital or nitrous oxide. This sedation also prevented a decrease in uterine blood flow when stress was repeated. (AM. J. OBSTET. GYNECOL. 134:270, 1979.)

THE EFFECTS of obstetric anesthesia on the fetus have been extensively investigated during the past decade. In contrast, scant attention has been paid to the possible adverse fetal effects of maternal apprehension and pain, which frequently occur when medication is withheld during labor and delivery. Previous reports have shown that maternal excitability may lead to acute fetal distress in the rhesus monkey.[1–3] It was postulated that the observed fetal asphyxia was due to an increased sympathetic activity in the mother resulting in enhanced uterine contraction and impaired uteroplacental perfusion. Indeed, it has been demonstrated that intravenous infusion of catecholamines into the mother can reduce uteroplacental blood flow in the sheep[4–6] and lead to severe fetal asphyxia in the rhesus monkey.[7]

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The present study on pregnant baboons was carried out as part of our continuing series of investigations on the influence of maternal pain and agitation upon the fetus.

Material and methods

A total of 25 experiments were performed on 17 pregnant baboons (*Papio* hybrid) with their fetuses at gestational ages ranging from 146 to 171 days (term 185 days). Initially, the animals were operated on under nitrous oxide and halothane anesthesia.[1] Catheters were placed in the maternal femoral artery and vein. In the fetus, either a carotid artery and jugular vein or a femoral artery and vein were catheterized at hysterotomy. Maternal and fetal ECG electrodes were applied, and thermistor probes were placed in the fetal esophagus and maternal colon. A catheter was also placed in the amniotic cavity in order to monitor intra-amniotic pressure. In eight experiments a pulsed Doppler flow transducer was implanted around the ascending branch of the uterine artery. Maternal core temperature was kept at approximately 38° C by means of a heating pad and an overhead source of infrared radiation. Maternal and fetal arterial pressure and heart rate as well as flow rate in a uterine artery and intra-amniotic pressure were continuously recorded. The heart rate was measured using either a cardiotachometer from the arterial pulse pressure or the R wave of the ECG. Uterine blood flow was measured

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Table I. Control values (mean ± SE) of maternal and fetal pH and blood gases, mean arterial pressure, and heart rate

	Mother (N = 25)	*Well-oxygenated fetus (N = 16)*	*Asphyxiated fetus (N = 9)*
pHa	7.46 ± 0.011	7.32 ± 0.014	7.26 ± 0.018*
$Paco_2$ (mm Hg)	30 ± 1.5	43 ± 1.9	47 ± 4.0
Base deficit (mEq/L)	1.2 ± 0.59	4.3 ± 0.62	6.2 ± 1.5
Pao_2 (mm Hg)	98 ± 9.3	30 ± 1.8	22 ± 2.1†
Sao_2 (%)	100	56 ± 3.1	29 ± 2.5‡
Mean blood pressure (mm Hg)	113 ± 2.6	48 ± 1.7	50 ± 1.5
Heart rate (beats/min.)	132 ± 4.2	184 ± 3.5	186 ± 10.0

*P < 0.05 compared with well-oxygenated fetus.
†P < 0.02 compared with well-oxygenated fetus.
‡P < 0.01 compared with well-oxygenated fetus.

using an ultrasonic pulsed Doppler system, and blood velocity change was expressed in percent from the control value.[8] Uterine activity was expressed in Montevideo units (MVU).[9] Blood samples were obtained simultaneously from the maternal and fetal artery at frequent intervals and analyzed for pH, Pco_2, and Po_2 using Radiometer microelectrodes and a Radiometer gas analyzer. The base deficit was calculated using the Siggaard-Andersen nomogram. The oxygen saturation (Sao_2) was estimated using the nomograms for adult and fetal baboons.[10]

Postoperatively, the animal was placed in the semilateral position and lightly restrained. She was sedated with nitrous oxide (75% to 80% in oxygen), and ventilated mechanically in order to maintain maternal arterial pH values between 7.38 and 7.48. The animals were allowed to recover for at least two hours after the hysterotomy (control period), after which they were subjected to stressful stimulation. The fetuses were divided into two groups according to their acid-base state prior to the study. On 16 occasions the fetuses were well oxygenated, a mean pHa being 7.32 ± 0.014 (SE) and Sao_2, 56% ±3.1%. In the remaining nine experiments the fetuses were acidotic and hypoxemic, with a mean pHa of 7.26 ± 0.018, and Sao_2 of 29% ± 2.5% (asphyxiated group).

During the experiment the gas mixture of nitrous oxide and oxygen was replaced by room air, but positive-pressure ventilation was maintained. After the mother was completely awake, a bright light was shone on her face (nine experiments) or a rubber-covered clamp was applied to a toe (16 studies) for 5 to 20 minutes (average 15 minutes). Similar stimuli were applied again following readministration of nitrous oxide and oxygen. On five occasions the mothers were given an intravenous injection of pentobarbitol, 2 to 3 mg/kg prior to or during stimulations. All results were analyzed using the paired t test and considered statistically significant when P values were less then 0.05.

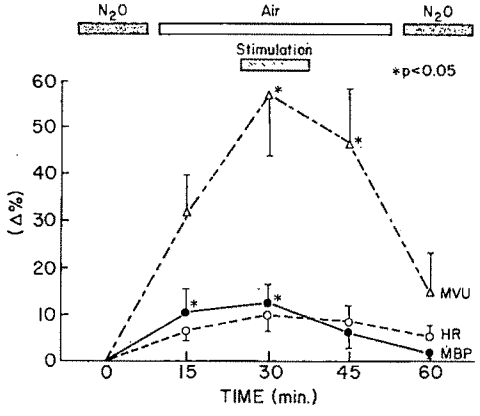


Fig. 1. Proportional changes in uterine activity, expressed in Montevideo units (MVU), maternal heart rate (HR), and mean arterial blood pressure (MBP) during air breathing and stressful stimulation. Increased MVU and MBP during stress were statistically significant compared to prestress values.

Results

Mother. The control values of maternal pH and blood gases, blood pressure, and heart rate prior to each stress experiment are summarized in Table I. After 3 to 5 minutes of air breathing, maternal arterial pressure began to rise significantly ($P < 0.05$) and remained elevated throughout the stimulation. The blood pressure, which was 113 ± 2.5 mm Hg during the control period, rose to 123 ± 3.4 mm Hg during air breathing and to 127 ± 4.5 mm Hg during stressful stimulation. The rise in blood pressure was accompanied by a slight increase in heart rate from 132 ± 4.2 to 141 ± 5.9 beats/minute during air breathing and to 143 ± 5.2 beats/minute during stimulation (Fig. 1). In eight instances sinus arrhythmia was observed during agitation. During air breathing the blood flow, mea-

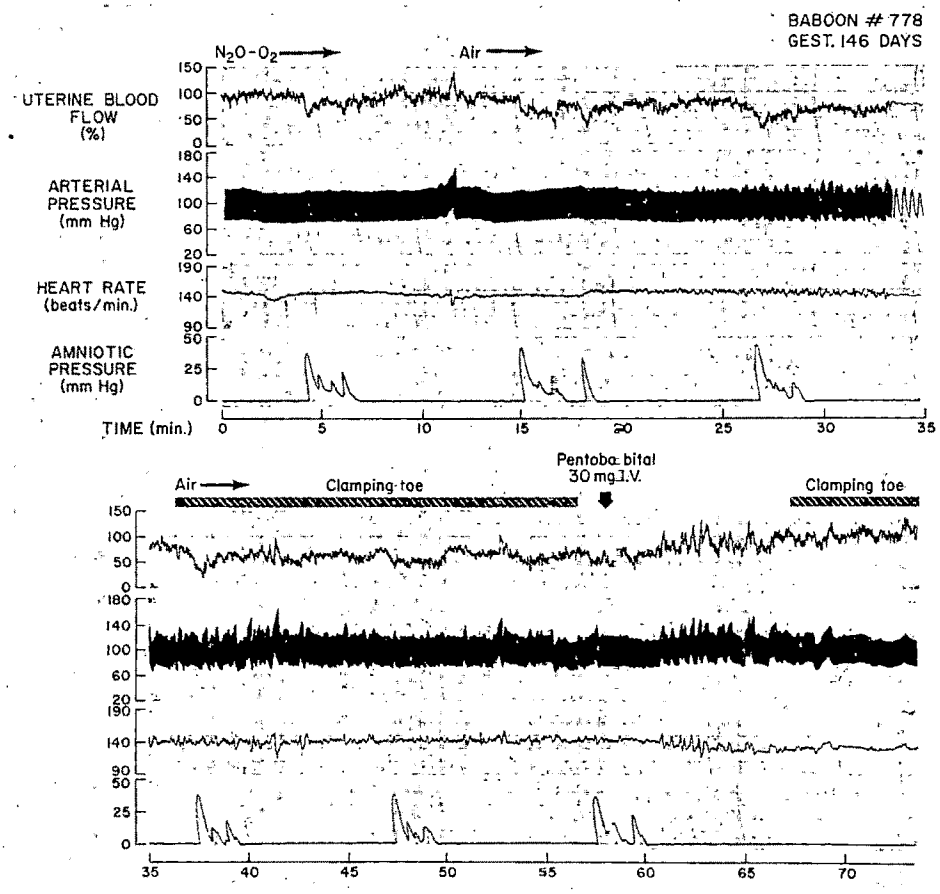


Fig. 2. Typical recording of uterine artery blood velocity (uterine blood flow), maternal arterial pressure and heart rate, and intra-amniotic pressure during air breathing, toe clamping, and following administration of pentobarbital. Note the reduction of blood flow during air breathing. The reduction became more profound during the toe clamping while the animal was breathing air. These changes were accompanied by irregular heartbeat. The toe was clamped again after administration of pentobarbital, but blood flow did not decrease with this stress.

Table II. Changes in maternal arterial blood pressure, heart rate, and uterine artery blood velocity during stress in eight experiments (percent change from control)

	Control (N_2O-O_2)		*Air*			*Stimulation (air)*			*Stimulus removed (air)*			*Recovery (N_2O-O_2)*		
Exp. No.	*MBP (mm Hg)*	*HR (bpm)*	*MBP (%)*	*HR (%)*	*UBF (%)*	*MBP (%)*	*HR (%)*	*UBF (%)*	*MBP (%)*	*HR (%)*	*UBF (%)*	*MBP (%)*	*HR (%)*	*UBF (%)*
1*	118	155	+13	+7	−7	+10	+18	−25	+5	+2	−8	+2	0	+20
2*	96	120	+5	0	−21	+10	+4	−3[illegible]	+8	+8	−11	−3	0	0
3*	132	130	+4	+8	−11	+8	+10	−56	+2	+2	−8	−2	+4	0
4†	117	110	+5	+14	−33	+23	+20	−45	—	—	—	—	—	—
5†	118	115	+8	+11	−28	+19	+21	−6	+8	+12	−21	+2	0	+18
6†	92	130	+8	0	−25	+8	+7	−5[illegible]	—	—	—	—	—	—
7†	121	120	+13	+9	−23	+18	+14	−5[illegible]	+10	+9	−20	+10	+9	+10
8†	130	135	+8	+4	−11	+19	+5	−7[illegible]	+10	+15	−11	−1	0	+7
Mean	116	127	+8	+7	−20	+14	+12	−5[illegible]	+6	+8	−13	+2	+2	+9
SE	5.1	5.0	1.2	1.8	3.3	2.1	2.4	3.4	1.6	2.2	2.4	1.9	1.5	4

MBP = mean arterial blood pressure; HR = heart rate; UBF = uterine blood flow.
*Light.
†Toe clamp.

sured in eight experiments, decreased by 7% to 33%. As much as a 70% reduction from the prestress level was observed during stimulation (Table II). Following readministration of nitrous oxide or injection of pentobarbital, the blood flow returned to control levels, and it did not decrease when the stimulus was applied again. A typical recording of changes in the blood flow during stress, before and after intravenous administration of 2 mg/kg pentobarbital, is depicted in Fig. 2. All animals showed mild to moderate spontaneous uterine activity with a mean of 90 ± 8.2 MVU at the end of the control period. Replacement of nitrous oxide with air caused an increase in amplitude and frequency of uterine contractions; the mean MVU rose to 119 ± 11.4 (31% ± 7.9% of control) (Fig. 1). Further increase ($P < 0.01$) to 145 ± 16.3 MVU (59% ± 13.0%) occurred during the stimulation. Elevated uterine activity persisted ($P < 0.05$) even after the stimulus was removed; 130 ± 21.3 MVU (44% ± 12.3%). Following readministration of nitrous oxide for 5 to 10 minutes, the uterine activity declined to a mean MVU value of 104 ± 15.4 (16% ± 8.3%). The maternal acid-base state remained essentially unchanged throughout the experiment. During the period of stimulation at which time uterine activity, blood pressure, and heart rate altered most significantly, values were pHa, 7.44 ± 0.011; $Paco_2$, 29 ± 1.5 mm Hg; base deficit, 3.0 ± 0.68 mEq/L; Pao_2, 97 ± 8.1 mm Hg, and Sao_2, 100%.

Fetus. The indicators of fetal condition prior to stress are shown in Table I. The most notable fetal changes during maternal agitation were in heart rate and arterial oxygenation, particularly in the asphyxiated group (Fig. 3). In the well-oxygenated fetus, heart rate remained essentially unchanged in the 15 minutes following discontinuation of nitrous oxide, but it fell from the prestress value of 184 ± 3.5 to 170 ± 6.9 beats/minute during stressful stimulation. However, in the asphyxiated fetus, it had already fallen from 186 ± 10.0 to 173 ± 6.7 beats/minute during air breathing, and further decreased to 150 ± 4.8 beats/minute ($P < 0.05$) during stress. Fetal Sao_2 fell from 56% ± 3.1% to 44% ± 4.4% during air breathing and 42% ± 4.6% ($P < 0.05$) with stimulation in the well-oxygenated group. In the asphyxiated group, Sao_2 fell from 29% ±2.5% to 22% ± 2.9% following air, and to 20% ± 2.6% ($P < 0.05$) with stress. In both groups of fetuses the heart rate and Sao_2 began to return to the prestress levels after removal of the stimulus while the mothers continued to breathe air. Fetal arterial pressure and acid-base state remained relatively stable throughout the experiment. The lowest mean pHa found during maternal stress was 7.23 ± 0.052 in the well-oxygenated group and 7.20 ± 0.032 in the asphyxiated group.

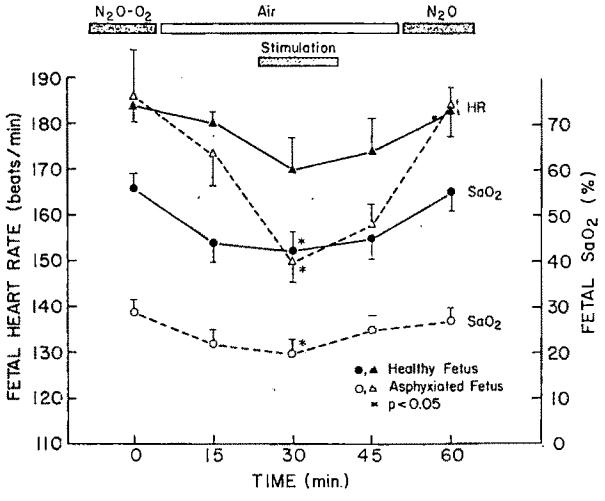


Fig. 3. Changes in fetal heart rate and arterial oxygenation during air breathing and maternal stress. Solid symbols and solid lines represent the well-oxygenated group; open symbols and broken lines, the asphyxiated group. Significant fall in heart rate and Sao_2 are seen during maternal stress in the asphyxiated fetuses.

A typical experiment of shining a bright light into the mother's eyes is seen in Fig. 4. Maternal blood pressure increased and heartbeat became irregular during air breathing. These symptoms were even more pronounced when the light was placed close to her face. Fetal response was minimal during air breathing, but heart rate, arterial pH, and oxygenation decreased following the light. Those variables recovered following readministration of nitrous oxide.

Clamping the mother's toe during air breathing resulted in maternal and fetal responses similar to those produced by the light (Fig. 5). Maternal agitation caused a marked fall in the fetal heart rate (from 190 to 138 beats/minute), pHa, and Sao_2. These values returned gradually toward prestress levels after removal of the clamp.

Comment

These experiments have demonstrated that removal of sedation and exposure to stressful stimuli, such as bright light and pain in the pregnant baboon, can lead to an increase in uterine activity and a reduction in flow rate in a uterine artery. As a result, a decrease in fetal heart rate and oxygenation may occur, particularly in an already asphyxiated fetus. When maternal agitation was eliminated by administering nitrous oxide or pentobarbital, uterine perfusion and the fetal condition improved. The study was performed in a semi-acute

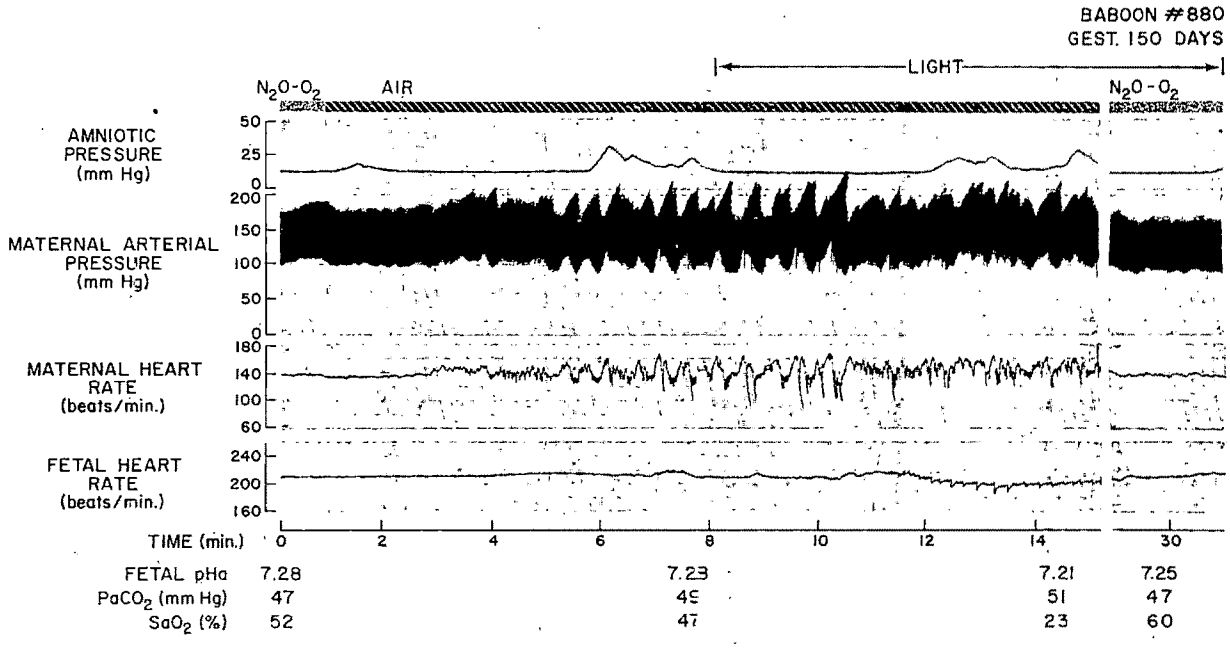


Fig. 4. Typical recording of intra-amniotic pressure, maternal arterial pressure and heart rate, and fetal heart rate during air breathing and exposure to a bright light. Note the decreasing fetal heart rate after shining a light on the mother's face. This was associated with a marked fall in fetal pHa and Sao_2.

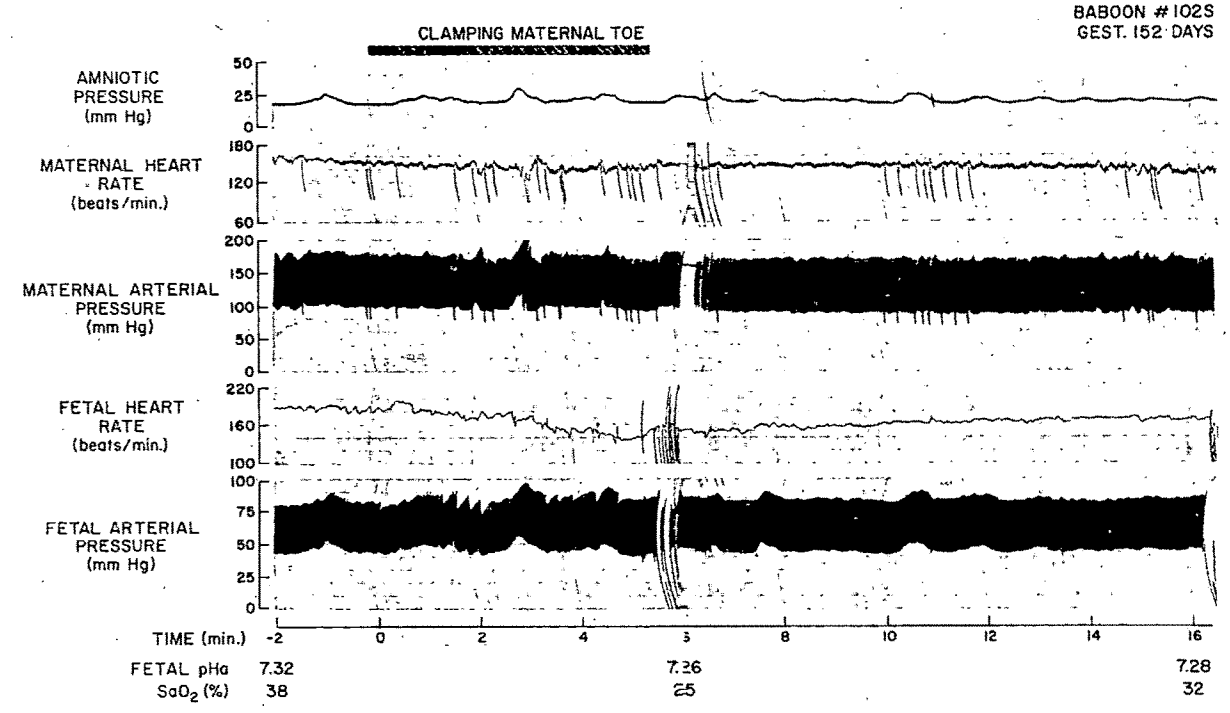


Fig. 5. A segment of the record in which intra-amniotic pressure, heart rate, and blood pressure of the mother and fetus are recorded. Stress was produced by clamping of the mother's toe. As the mother became agitated, there was a fall in fetal heart rate and a decrease in fetal arterial oxygenation, as seen in the bottom record. Note that fetal arterial pressure increases during uterine contractions as increased intra-amniotic pressure is transmitted to the fetus.

preparation, and nitrous oxide had been administered during the control period. Therefore, it might be argued that the condition of the animal during the control period was quite different from the unsedated human subject during labor and delivery. The quality and degree of pain which the baboon is capable of appreciating remain difficult to assess and may be quite unlike the capacity of humans. Nevertheless, reduction of uteroplacental perfusion during the stress undoubtedly plays the main role in fetal hypoxemia as a consequence of decreased oxygen availability. Recently, we have observed similar results in unanesthetized, chronically instrumented pregnant sheep. A marked decrease in uterine blood flow and an increase in arterial pressure occurred during maternal agitation resulting from clamping the earlobe. These changes were prevented by administering diazepam prior to clamping. It has been shown that intravenous infusion of catecholamines into pregnant sheep has resulted in a reduction in uteroplacental blood flow.[4-6] Epinephrine and norepinephrine produced endogenously in response to stress might be expected to show similar effects. In fact, we have some recent data, as yet unpublished, that there is a significant increase in plasma epinephrine and norepinephrine levels during stress in the pregnant baboon. Another study[11] on pregnant women has shown that plasma epinephrine levels increase during labor and delivery; epinephrine values rapidly decreased after delivery. Increased epinephrine levels were significantly reduced after establishing regional anesthesia.

In summary, it can be concluded that maternal agitation may be harmful to the fetus. Under these circumstances, sedation or pain relief in the mother appear to be beneficial not only to the mother but also to the integrity of uteroplacental circulation and, ultimately, to fetal well-being.

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Effect of maternal glucose load on fetal activity

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The effect of a MGL upon fetal activity has been studied in 39 normal and 54 high-risk pregnant patients between 30 and 42 weeks' gestation. The perinatal morbidity and mortality rates were significantly lower in the group showing an increase in fetal activity following a MGL. It is suggested that this may be useful for identifying the fetus at risk. (AM. J. OBSTET. GYNECOL. 134:276, 1979.)

GLUCOSE is an important source of fetal energy, fetal glucose levels being dependent on maternal supply. Therefore, fetal energy expenditure is, in part, controlled by availability of maternal glucose. A study was undertaken to ascertain the effect of a standard maternal glucose load (MGL) upon fetal activity in normal and high-risk pregnancies.

Material and methods

From the Obstetrical Service of the University of Illinois Hospital in Chicago, 39 normal and 54 high-risk pregnant patients between 30 and 42 weeks' gestation were selected for this study (Table I). All tests were performed between 08:00 and 11:00 A.M. after an overnight fast. Maternal fasting blood sugar (FBS) levels were determined in all cases.

Following a 1 hr baseline recording of fetal heart rate (FHR) and fetal movements (FM), all patients were given either a 100 gm oral glucose load or a 0.5 gm/kg intravenous glucose load. Since the intravenous rather than the oral route is preferred for a glucose tolerance test at our institution, an intravenous load was administered whenever a glucose tolerance test was clinically indicated. Five patients in the normal pregnancy group and 22 in the high-risk group had an intravenous glucose load (29.1%). The remaining 66 patients (70.9%) had an oral glucose load. Maternal blood glucose levels were determined at 1 and 2 hours after oral glucose load and at 15 min intervals for 1 hour after the intravenous load. In all cases FHR and FM were recorded for 2 hours after glucose load. In addition, the morning after the MGL loading test, every fifth patient in both the normal group (8 patients) and the high-risk group (10 patients) underwent a prolonged 3 hours nonstressed monitoring (NSM) without MGL.

The interval time between the MGL and delivery varied between 4 and 22 days. Hewlett Packard equipment was used to monitor FHR and FM. Fetal movements were recorded by way of an external tocodynamometer placed on the maternal abdomen and also identified by the mother verbally and/or by activating an event-marker connected to the uterine channel, thus producing an upward deflection of the stylus.

FHR was obtained through an indirect fetal electrocardiograph (HP 15174A) from the maternal abdomen in 22 normal patients and 40 high-risk patients (66.7%), and by way of an ultrasound amplifier (HP 15180) in the remaining 17 normal patients and 14 high-risk patients (33.3%). The fetal heart beat-to-beat variability as well as reactivity to FM were noted. The percentage of FHR accelerations to FM was also determined.

Two types of fetal movements were identified: (1) isolated movements (I), 12 sec or more apart from each other and (2) multiple movements (M), a series of

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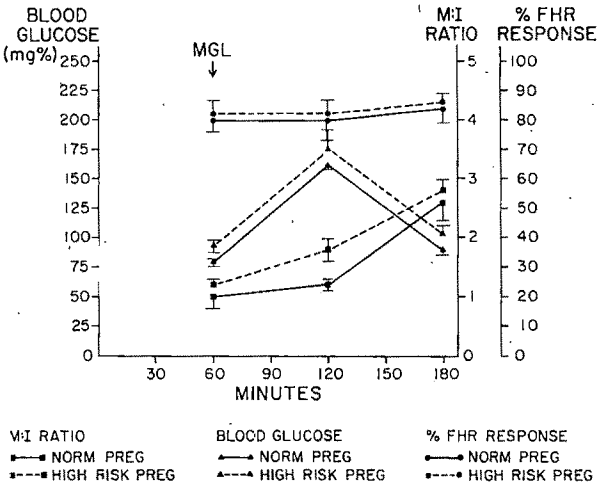


Fig. 1. Normal oral MGL test in normal and high-risk pregnancies. The values for the M:I ratio and percent of FHR response during the first recording hour are represented by the S.D. plotted at 60 min.

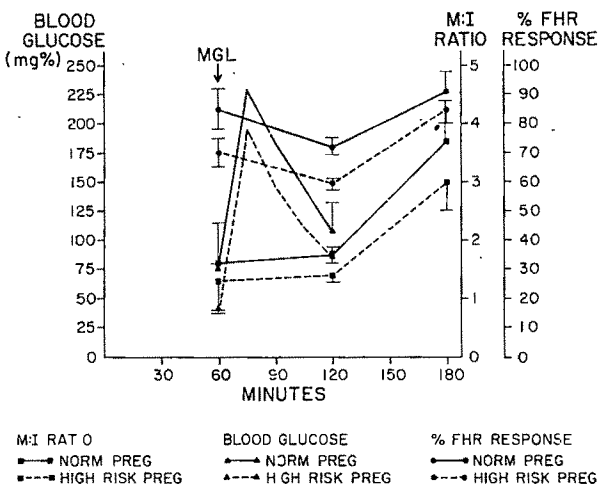


Fig. 2. Normal intravenous MGL test in normal and high-risk pregnancies. Data as in Fig. 1.

Table I. MGL test

Clinical material	*No.*
Normal pregnancies	39
Diabetes "A"	12
Diabetes "B"	8
Diabetes "C"	1
Chronic hypertension	8
Third-trimester bleeding	6
Rh sensitization	5
Pre-eclampsia	4
Renal disease	2
Hemoglobinopathies	2
Other	6
Total	93

Table II. MGL and perinatal outcome

M:I increase (%)	*Incidence*	*Perinatal outcome**
>100	85/93 (91.4%)	Abnormal 1/85—1.18%† Normal 84/85-98.82%
<100	8/93‡ (8.6%)	Abnormal 7/8-87.5% Normal 1/8-12.5%

*$p < 0.001$; binomial expansion test.
†Exchange transfusion Rh sensitized.
‡See Table III for clinical details.

isolated movements less than 12 sec apart from each other with an average of four movements per group. For each hour the ratio between multiple and isolated movements (M:I ratio) was calculated.[1] Estriols, hPL, OCT, and labor monitoring tracings were compared with the results of the MGL.

Results

Based on the presence or absence of M:I ratio change, two groups of patients were identified. In the first group (normal MGL test—91.4%), regardless of whether the glucose load was administered orally (Fig. 1) or intravenously (Fig. 2), there was a marked increase in the number of multiple movements which increased the M:I ratio by more than 100 per cent over the fasting level by the end of the second hour after MGL. In the second group (abnormal MGL test—8.6%), the fetal activity remained unchanged and the M:I ratio did not increase under similar experimental conditions (Figs. 3 and 4). The perinatal mortality and morbidity rates were significantly higher ($p < 0.001$) in the second group (Table II). Both normal and high-risk pregnancies were included in the first group; the second group comprised only high-risk pregnancies. The peak of the maternal blood glucose preceded the increase in the M:I ratio in the first group. In the second group the fasting M:I ratio was not affected by the maternal rise in blood glucose level. The percentage of FHR response to FM did not change from the fasting to the fed state in the first group. In the second group, it was initially lower in comparison with the first group, increased briefly following the MGL, and returned to the fasting level thereafter.

In both groups the nonstressed monitoring tracings were interpreted as being of the reactive pattern[9] with the exception of a sinusoidal pattern in a severly affected erythroblastotic infant who died in utero soon thereafter. Prolonged 3 hr NSM sessions during fasting state showed that the M:I ratio did not vary with time (Fig. 5). The estriols, hPL, OCT, and labor monitoring

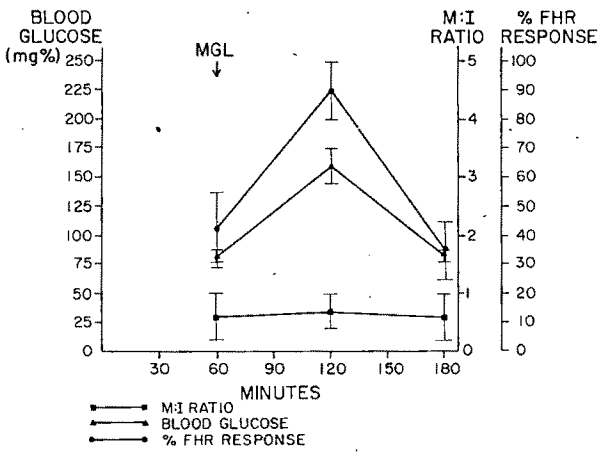


Fig. 3. Abnormal oral MGL test. Only high-risk pregnancies comprised in this group. Data as in Fig. 1.

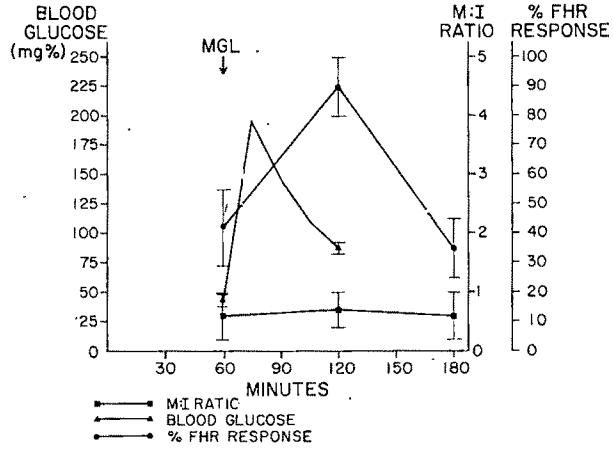


Fig. 4. Abnormal intravenous MGL test. Only high-risk pregnancies comprised in this group. Data as in Fig. 1.

Table III. Estriols, hPL, OCT, and labor monitoring data in cases with abnormal MGL and/or perinatal outcome

Perinatal outcome	*Clinical diagnosis*	*Gestation (wk)*	*MGL*	*Days to delivery past MGL*	*E_3* (mg/24 hr)*	*hPL* (μg/ml)*	*OCT†*	*Labor monitoring*
Erythroblastosis	Rh−	37	Normal‡	6	14	6	Neg.	Normal
SGA—normal course	Pre-eclampsia	38	Abnormal	14	9	12	Neg.	Transient early deceleration
SGA-RDS	Renal disease	36	Abnormal‡	11	10	9	Neg.	Early deceleration, second stage
IUGR-SGA—hypoglycemia	Chronic hypertension	37	Abnormal‡	10	13	5	Neg.	Normal
SGA—normal course	SS disease	39	Abnormal	9	8	6	Pos.	Variable deceleration, cord × 2
LGA-RDS	Diabetes "B"	38	Abnormal‡	4	8	11	Neg.	Normal
Normal	Diabetes "B"	38	Abnormal‡	7	18	7	Neg.	Normal
Premature RDS, neonatal death	Placenta previa	36	Abnormal‡	8	8	N.D.§	N.D.	Cesarean section
Stillbirth, erythroblastosis	Rh−	30	Abnormal	4	N.D.	N.D.	N.D.	N.D.

*Last value prior to delivery.
†<7 days prior to delivery.
‡Indirect FECG.
§N.D., not done.

tracings in the nine cases with either an abnormal perinatal outcome, abnormal MGL, or both are shown in Table III. There was only one abnormal MGL with a normal perinatal outcome in a patient with Class B diabetes. Of the eight cases with an abnormal perinatal outcome, seven has an abnormal MGL test. In only one case the OCT was positive <7 days prior to delivery. Estriols, hPL, and labor monitoring tracings were all within normal limits. The MGL result did not appear to correlate with any pregnancy risk in particular (Table IV).

Comment

The difference in the perinatal morbidity and mortality rates in the two groups identified by the MGL test would suggest the fetuses in the first group to be in homeostatic balance and those in the second group to be at risk. Maternal glucose is the main source of fetal glucose,[5, 11] this being fundamental for the maintenance of brain and heart functions[2] and a major source of fetal energy.[12] Maternal starvation, on the other hand, alters the glucose supply to the fetus by reducing the maternal-glucose concentration difference[12] and fetal glucose uptake.[2, 6] Furthermore, hypoxemic fetuses show no increase in glucose uptake with either increasing maternal glucose levels or increasing glucose gradients.[3] One could therefore speculate that in the presence of an increase in glucose inflow as a result of maternal glucose load in fasting mothers, the fetuses in the first group replenished their reserves and subsequently enhanced their activities, whereas the fetuses in the second group probably either use the glucose for

Table IV. Correlation between pregnancy course and M:I ratio increase after MGL

Risk	Nos.	Increase of M:I. >100% No.	>100% %	<100% No.	<100% %
Normal	39	39	100	—	
Diabetes A	12	12	100	—	
Diabetes B	8	6	75	2	25
Diabetes C	1	1	100	—	
Chronic hypertension	8	7	87.5	1	12.5
Third-trimester bleeding	6	5	83.4	1	16.6
Rh sensitization	5	4	80	1	20
Pre-eclampsia	4	3	75	1	25
Renal disease	2	1	50	1	50
Hemoglobinopathies	2	1	50	1	50
Other	6	6	100	—	
	93 (100%)	85	91.4	8	8.6

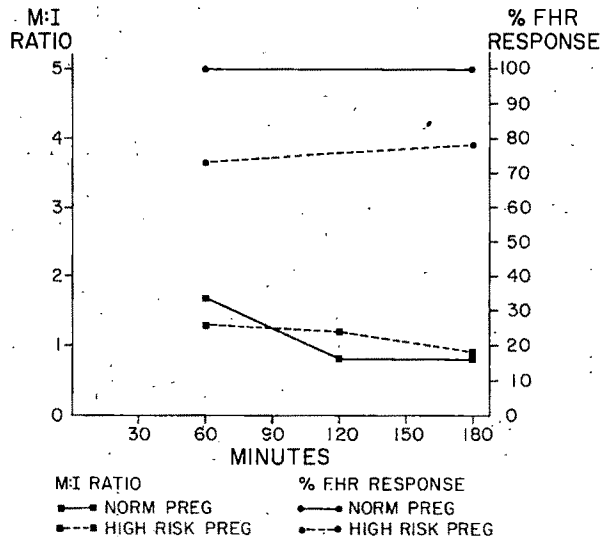


Fig. 5. Prolonged NSM in the fasting state without MGL in normal and high-risk pregnancies. Data as in Fig. 1.

functions more important than physical activities or may not be able to benefit from the availability of glucose altogether.

The increase of fetal activity following MGL observed in this study is in agreement with the report of Spellacy and colleagues.[13] This increase in fetal activity is characterized by an increase in multiple movements with the consequent increase in the M:I ratio. The nature of these multiple movements, however, is not clear. One suggestion is that multiple movements may represent fetal respiratory movements, total body movements, or a combination of both.[1, 4, 8, 14] However, the effect of a glucose load on fetal respiratory movements, assuming these to be a major component of multiple movements, is unsettled since some studies suggest a resumption of fetal breathing movements when hypoglycemia is corrected by glucose infusion[4, 8] and others have not been able to observe this phenomena.[7] It should be noted, however, that the stressful experimental conditions of insulin-induced hypoglycemia[7] are not entirely comparable to the fasting state and glucose administration of this or other studies.[8, 13] The lack of increase of fetal activity observed in the second group is in agreement with the report of a decrease in fetal breathing movements[4] and a decrease of total movements[10] in compromised fetuses.

Following glucose loading, the peak of the fetal activity increase as represented by the M:I ratio was delayed considerably with respect to the peak of the maternal glucose levels. It is therefore postulated that the triggering factor responsible for the increase in fetal activity is the glucose load through some physiologic process rather than an immediate result of a "glucose shock" or some other unphysiologic mechanism. In abnormal MGL tests, this mechanism is probably impaired. Prolonged NSM without MGL showed the M:I ratio not to increase spontaneously with the passage of time.

All but one of the tracings in these studies were of the reactive pattern variation[9] and were of no predictive value except for the nonreactive sinusoidal pattern in the one case of intrauterine fetal death in a severly erythroblastotic fetus. However, the variation in the test-to-delivery time in this study may be responsible for this lack of correlation. The significance of the transient improvements in the percentage of FHR accelerations to FM following MGL in the abnormal group on the one hand, and the significance of the low percentage of FHR accelerations to FM in the fasting state when compared to the normal group, remain to be established. These findings however, suggest that more sensitive definitions of nonstressed reactivity patterns are needed.

The data of estriols, hPL, and OCT were not notable for their predictive value of perinatal morbidity and death in the abnormal MGL group, except for a positive OCT. However, the MGL was abnormal in seven out of the eight cases with an abnormal perinatal outcome. Larger series may clarify if fetal activity enhancement following maternal MGL may be disturbed earlier than the hormonal or stress assessments, in which case it could become an important tool for early recognition and detection of fetal compromise, particularly since the lack of response does not seem to be characteristic of a given risk factor only. Fetal hyperglycemia may increase plasma lactate and decrease blood pH, thus iatrogenically causing acute fetal distress.[11] As it may have been determined by the presence of fetal bradycardia, this did not occur in this series.

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The dehydroepiandrosterone loading test

III. A possible placental function test

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The dehydroepiandrosterone loading test (DLT) has been used in a small population of normal and high-risk obstetric patients, to date, in an attempt to develop a dynamic test of placental function. In spite of its limited applications, it has shown reliability in discriminating, with statistical significance, between high-risk pregnancies that result in normally grown, undistressed infants, and high-risk pregnancies that result in infants showing signs of placental insufficiency. The present report expands the study population by presenting our data on 40 loading tests performed in 37 high-risk and normal obstetric patients. Results of 19 of these DLT's have been previously reported and are included herein for statistical analysis. The DLT utilizes an excess substrate load of dehydroepiandrosterone to assess the maximum capability of the placenta to convert it to estrogen. Although our previous report did not show false positive or negative results in the conversion rates, the present results (40 DLT's) found two (2 out of 17) false positives (12%) and two (2 out of 19) false negatives (11%). The highly significant correlation between DLT result and pregnancy outcome seen previously[2] was preserved. In addition, the data of another five DLT's in four patients are presented. This group includes a pregnancy with a fetus with multiple congenital malformations, two patients with intrauterine fetal death, and a nonpregnant woman. The results are not included in the statistical analysis, but discussion of these results has interesting pathophysiologic implications.
(AM. J. OBSTET. GYNECOL. 134:281, 1979.)

PREVIOUS work from this group[1, 2] has demonstrated that the dehydroepiandrosterone loading test (DLT) may be a valid indicator of placental function. In the limited population studied, the DLT has been shown to be capable of discriminating between high-risk pregnancies resulting in normally grown, undistressed infants, and those resulting in infants with signs of chronic placental insufficiency ($p = 0.001$).

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In addition, the DLT has been shown to be capable of discriminating between normal obstetric patients and high-risk obstetric patients who delivered infants with signs of chronic fetal distress.[2]

Chronic placental insufficiency was considered to be present when: (1) the birth weight of the newborn infant was below the tenth percentile for gestational age; or (2) the birth weight was below the twenty-fifth percentile, but with a positive oxytocin challenge test (OCT), or with signs of acute fetal distress during labor; or (3) complete clinical cessation of fetal growth for a period of four weeks or more during the prenatal course as judged by fundal height or ultrasonographic determination of biparietal diameter.

This work was based upon the animal model studies by Pupkin and associates[5] in our group, which in turn was stimulated by Lauritzen's[5] clinical studies utilizing DHEA-S and urinary estrogen determination.[1, 2, 5]

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Table I. Patient and DLT distribution by groups

Group	*Group description*	*No. of patients*	*No. of DLT's*
A	Normal obstetric patients with good pregnancy outcomes	5	5
B	High-risk obstetric patients whose infants showed signs of acute and/or chronic placental insufficiency	13	13
C	High-risk obstetric patients whose infants showed signs of acute placental insufficiency only	4	4
D	High-risk obstetric patients with good pregnancy outcomes	13	13
E	*Miscellaneous group:*	4	5
	Nonpregnant patient	(1)	(1)
	Patient with IUFD*	(2)	(3)
	Patient whose infant had multiple congenital anomalies	(1)	(1)
Total		37†	40

*IUFD = Intrauterine fetal death.

†The patient column adds to 39, since some patients changed groups between their first and second tests (see "Comment").

Table II

Patient	*Group* and gestational age at test time*		*High-risk factors and complications of labor and delivery*	*EGA at birth (wk.)*	*Birthweight*		*Apgar scores (1 min./ 5 min.)*	*"b" Conversion rate constant ($\times 10^{-3}$ min.$^{-1}$)*
					Grams	*Percentile*		
S.S.E.	A	37	None	38	3,200	50-75	8/9	8.5
L.B.R.	A	36½	None	37	3,400	75-90	7/9	5.0
L.C.O.	A	34	None	38	2,990	50	8/9	4.2
C.L.O.	A	34	None	37	2,480	25-50	7/9	5.8
P.C.H.	A	35½	None	39½	3,245	50-75	?	4.9
D.S.H.	B	30	Severe pre-eclampsia; fetal brady-tachycardia in labor	32½	1,300	10-25	8/?	1.5
M.T.H.	B	34	History of IUFD; fetal bradycardia during labor	35	1,925	10-25	7/9	0.3
E.R.I.	B	37½	History of IUGR; size-date discrepancy; meconium staining; oligohydramnios	38	1,320	<10	8/8	0.8
D.S.C.	B	36	Severe pre-eclampsia; size-date discrepancy; fetal bradycardia prior to labor	36	1,900	10	8/10	1.5
R.L.A.	B	31½	Cessation of fundal height growth for 6 wk.; no fetal distress after resumed growth	40	3,460	50-75	9/10	1.8
F.C.O.	B	37	Mild pre-eclampsia; size-date discrepancy; no fetal distress	38	2,170	<10	8/10	1.6
B.N.G.	B	37	Cessation of fundal height growth for 6 wk.; no fetal distress	37½	2,300	10	8/9	1.5
J.S.T.	B	29½	Cessation of fundal height growth for 4 wk.; mild pre-eclampsia; no fetal distress	32	1,275	15	2/?	0.3
J.P.E.†	B	33½	Cessation of fundal height growth for 8 wk; premature labor	39	3,100	50	8/9	985.6
E.S.T.	B	39	Size-date discrepancy; no fetal distress	39	2,170	<10	3/7	0.2
M.H.A.	B	39	Size-date discrepancy; no fetal distress	39	2,010	<10	7/8	1.2
J.B.L.	B	38½	Size-date discrepancy; positive oxytocin challenge test	39½	2,900	25	10/10	1.2
S.C.A.†	B	32	Cessation of growth for 6 wk.; history of IUFD; no fetal distress	42	4,040	90	9/10	0.7
L.M.O.	C	37	Class A diabetes; size-date discrepancy; late decelerations	38	2,880	25-50	8/9	1.3
K.R.E.	C	37	History of IUFD; heavy meconium in labor	42	3,140	25-50	9/10	2.4
J.R.O.	C	37	Adrenogenital syndrome on prednisone; fetal bradycardia during labor	37	3,020	30	8/10	209.0

IUGR = Intrauterine growth retardation and IUFD = intrauterine fetal death.

*Patient groups as listed in Table I.

†Indicates two tests done on same patient.

? = Not recorded in chart.

Table II—Cont'd

Patient	Group* and gestational age at test time		High-risk factors and complications of labor and delivery	EGA at birth (wk.)	Birthweight		Apgar scores (1 min./ 5 min.)	"b" Conversion rate constant ($\times 10^{-3}$ min.$^{-1}$)
					Grams	Percentile		
J.P.E.†	C	39	Cessation of growth for 8 wk. with resumed growth; fetal bradycardia during labor	39	3,100	50	8/9	2.8
S.S.M.	D	34	Class B diabetes; hypertension; IUFD × 3; no signs of fetal distress prior to delivery	35	2,120	25-50	4/5	85.0
C.E.V.	D	33½	Class A diabetes; hypertension; no fetal distress	37½	2,780	25-50	?	4.5
M.L.E.	D	37	Hypertension; massive obesity; no fetal distress	40	4,320	>90	8/9	244.0
P.K.U.	D	33½	History of IUFD; size-date discrepancy; uterine inertia; no fetal distress	37½	2,550	25-50	8/9	591.0
H.A.L.	D	36	Class A diabetes; hypertension; history of IUFD; no fetal distress	36½	3,000	50-75	7/8	8.0
D.H.A.	D	31	Size-date discrepancy; cesarean section prior to labor	35	2,140	25-50	?	56.6
G.C.A.	D	37	History of postpartum eclampsia; postpartum eclampsia; no fetal distress	37	3,000	50-75	8/10	1.2
A.M.A.	D	32½	History of IUFD and IUGR; no fetal distress	36	2,720	50-75	9/10	325.8
N.R.I.	D	32½	History of IUFD; no signs of fetal distress prior to precipitous delivery	34	2,940	>90	1/4	3.7
J.M.C.	D	24	Anemia; chronic glomerulonephritis; hypertension; no fetal distress	34	2,415	75	9/10	8.9
J.A.	D	40	Size-date discrepancy; poor weight gain; no fetal distress	40	3,040	25	8/9	8.2
M.H.O.	D	38	Size-date discrepancy; no fetal distress	39	2,570	10-25	7/9	1.9
S.C.A.†	D	32	Resumed fundal height growth after 6 wk. of no growth; no fetal distress	34	4,040	>90	9/10	4.9
J.A.N.	E	29½	Class B diabetes; IUFD at 29 wk.	29+6	990	10-25	0/0	303.0
J.P.U.	E	—	Nonpregnant; taking Synthroid	—	—	—	—	0.04
V.F.R.	E	35	Cessation of fundal height growth for 3 wk.; Class A diabetes; multiple congenital anomalies	35	900	<10	3/3	36.1
M.W.I.†	E	36	Class B diabetes; massive obesity; IUFD at 35 wk.	37	2,460	25-50	0/0	4.5
M.W.I.†	E	37	Class B diabetes; massive obesity; IUFD at 35 wk.	37	2,460	25-50	0/0	3.0

IUGR = Intrauterine growth retardation and IUFD = intrauterine fetal death.
*Patient groups as listed in Table I.
†Indicates two tests done on same patient.
? = Not recorded in chart.

Our reason for continued interest in this work is that a simple, dynamic placental function test, which the DLT appears to be, with a specific predictive value, would provide a useful new tool to clinicians dealing with high-risk obstetric patients, questionable gestational age histories, or equivocal clinical fetal growth parameters.

Material and methods

All of the patients included in this study were identified by and cared for by the Division of Perinatal Medicine, Duke University Medical Center.

As stated previously, this study comprises a total of 40 DLT's in 37 patients, and includes 19 DLT's in 19 patients previously presented.[2]

Table I describes the patient groups studied.

Group A consists of five tests in five normal patients who had uneventful pregnancies and normally grown, undistressed infants.

Group B is composed of 13 tests in 13 high-risk patients who were diagnosed as having chronic placental insufficiency, defined as a birth weight below the tenth percentile, or a birth weight below the twenty-fifth percentile with a positive OCT or manifestations of acute

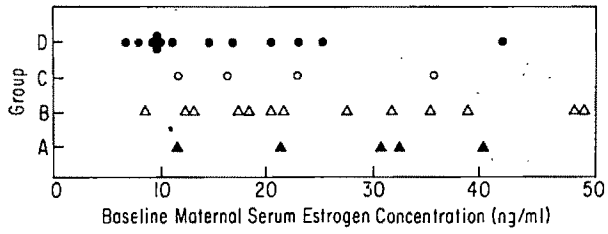


Fig. 1. Baseline maternal serum estrogen concentration (ng/ml) segregated by groups.

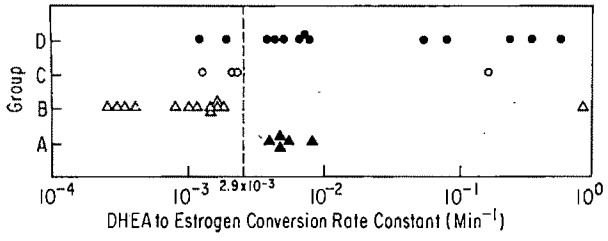


Fig. 2. DHEA to estrogen conversion rate constant ($min.^{-1}$) segregated by groups.

Table III. Baseline maternal serum estrogen concentrations of the patient groups described in Table I.

Group	*Mean (ng/ml)*	*Range (ng/ml)*
A	27.8	11.9-40.5
B	26.3	8.4-49.7
C	21.7	11.8-35.4
D	15.9	7.4-42.4
E	3.5	0.21- 6.0

Table IV. Baseline maternal serum estrogen concentrations: Statistical comparisons of the patient groups as described in Table I

	Group A	*Group B*	*Group C*	*Group D*
Group A	—	N.S.	N.S.	*
Group B	—	—	N.S.	*
Group C	—	—	—	N.S.
Group D	—	—	—	—

NS = not significant.
*$p < 0.05$.

fetal distress during labor, or a complete clinical cessation of fetal growth for a period of four weeks or more.

Group C contains four tests in four high-risk patients who developed fetal distress during labor, but delivered normally grown infants.

Group D consists of 13 tests in 13 high-risk patients who delivered normally grown, undistressed infants. While some of these patients were chosen because of size-date discrepancies, none exhibited discernible cessation of either uterine size or biparietal growth as estimated by ultrasonography.

Group E contains five DLT's in four patients. The patients in this miscellaneous group will be discussed individually and in detail. It includes one normal nonpregnant patient, two patients with intrauterine fetal death (IUFD), and one patient whose fetus had multiple congenital malformations. Table II presents each patient's high-risk factors, gestational age at the time of the DLT, birth weight, gestational age at the time of birth, and the study group to which the patient was assigned.

In all groups, gestational age was determined clinically by maternal menstrual history and its correlation with uterine size in early pregnancy. In addition, serial ultrasonography and maturity studies were used when needed. In newborn infants, gestational age was corroborated by the Dubowitz score and the percentile category determined by the chart of Lubchenco and colleagues.[3]

The protocol of the DLT is described in full elsewhere,[2] but in brief, comprises the intravenous injection of 25 mg DHEA (5-androsten-3β-ol-17-one*) prepared as a sterile solution of 5 mg DHEA/ml in ethanol-saline (1:1, v:v) by the Duke Hospital Pharmacy. Approximately ten minutes prior to the administration of DHEA, a control blood sample for hormonal analysis is obtained. The DHEA solution is injected as a bolus into the antecubital vein; injection time is fast, not lasting more than five seconds. The vein is then immediately flushed with 10 ml of normal saline. After infusion of the DHEA, 6 ml blood samples for hormone analysis are drawn at 5, 10, 7.5, 15, 30, 45, 60, and 180 minutes. All blood samples are drawn from the same intravenous line.

The DLT involves only a mild discomfort to the patient. This is produced by the ethanol contained in the vehicle, which causes momentary irritation and a burning sensation in the vein of injection. This is a variable phenomenon, however, never lasting for more than 30 seconds in our experience.

Prior to the initiation of the test, each patient signs an informed consent. The informed consent and study protocol have been approved by the Human Experimentation Committee at Duke University Medical Center.

Total serum estrogens are measured by radioimmunoassay using a slight modification (less serum) of the technique described by Aksel and associates[8, 10] which was developed and validated in our laboratory. The cross-reactivities of the antibody are: 80% with estrone,

*Steraloids, Inc., Pawling, New York.

Table V. DHEA-to-estrogen conversion rate constant in all groups as described in Table I

Group	*Mean ($min.^{-1} \times 10^{-3}$)*	*Range ($min.^{-1} \times 10^{-3}$)*
A	5.7	4.2-8.5
B	76.8	0.2-986.0
C	53.9	1.3-209.0
D	103.3	1.2-591.0
E	69.3	0.0-303.0

Table VI. DHEA-to-estrogen conversion rate constant statistical comparison by patient groups as described in Table I

	Group A	*Group B*	*Group C*	*Group D*
Group A	—	†	N.S.	N.S.
Group B	—	—	*	‡
Group C	—	—	—	N.S.
Group D	—	—	—	—

N.S. = Not significant.
*$p < 0.05$.
†$p < 0.01$.
‡$p < 0.001$.

100% with 17β-estradiol, 5% with estriol, and 0.0002% with DHEA.

The data are analyzed by fitting the mathematical representation of a physiologic model using a computer program. In brief, the model permits identification of the rate constant of DHEA to estrogen conversion using the DLT data and some explicitly stated assumptions as to the physiology of the fetoplacental unit. The model, its mathematical representation, and computer program are described in detail elsewhere.[1, 9]

Statistical significance is determined by means of the Mann-Whitney U test,[7] as discussed previously.[2] This test permits statistical comparison without requiring that the groups tested follow a normal or Gaussian distribution.[7]

Results

Baseline serum estrogens segregated by Groups A, B, C, and D. For comparison, total serum estrogen values obtained (basal values during the DLT protocol) are analyzed by groups. Tables III and Table IV illustrate their values and the lack of intergroup differences. Fig. 1 illustrates these data graphically.

DHEA to estrogen conversion rate constant values as segregated by Groups A, B, C, and D. The distribution of DHEA to estrogen conversion rate constants by group is shown in Table V. Fig. 2 illustrates that Group A had conversion rate constants tightly clustered between 4.2×10^{-3}, and 8.5×10^{-3} (the units of the conversion rate constant, $min.^{-1}$, are deleted for brevity).

Table VII. Patients for special discussion, DHEA-to-estrogen conversion rate constant as described in Table I

Patient	*Group*	*Gestational age at test time (wk.)*	*DHEA-to-estrogen conversion rate constant*
G.C.A.	D	37	1.2×10^{-3} $min.^{-1}$
M.H.O.	D	38	1.9×10^{-3} $min.^{-1}$
J.R.O.	C	37	209.0×10^{-3} $min.^{-1}$
J.P.E.	B	33½	986.0×10^{-3} $min.^{-1}$
J.P.E.′	C	38	2.8×10^{-3} $min.^{-1}$
S.C.A.	B	32	0.7×10^{-3} $min.^{-1}$
S.C.A.′	D	34	4.9×10^{-3} $min.^{-1}$

Table VIII. Group E patients (see Table I)

Patient	*Group*	*Gestational age at test time (wk.)*	*DHEA-to-estrogen conversion rate constant*
V.F.R.	E	35	36.1×10^{-3} $min.^{-1}$
M.W.I.	E	36 + 1 wk. IUFD	4.5×10^{-3} $min.^{-1}$
M.W.I.′	E	36 + 2 wk. IUFD	3.0×10^{-3} $min.^{-1}$
J.A.N.	E	29 + 2 wk. IUFD	303.0×10^{-3} $min.^{-1}$
J.P.U.	E	Nonpregnant	0.04×10^{-3} $min.^{-1}$

Note that most patients who were delivered of normal babies (Groups A and D) had DHEA to estrogen conversion rate constants greater than 2.9×10^{-3}, while most patients with compromised fetuses had values of less than 2.9×10^{-3}. Table VI presents the statistical intergroup comparisons. Note that, while the DLT could not discriminate between the normal patients (Group A) and the high-risk, good-outcome patients (Group D), it was able to distinguish both groups from the high-risk patients whose infants showed signs of chronic placental insufficiency (Group B).

Miscellaneous Group E results. The Group E patients are excluded from the above analysis since they deserve special attention, and cannot be compared with the other patients. Since no definite conclusion can be obtained from this miscellaneous group of patients, all individuals will be discussed separately. Information pertaining to these patients plus other patients deserving discussion (two Group B patients, one Group C patient, two Group D patients) may be found in Tables VII and VIII. The possible physiopathologic implications are presented in the "Comment."

Comment

Our first report[5] demonstrated the capability of the animal fetoplacental unit model to convert DHEA to estrogens. The same study showed a lower conversion capability when the fetus was compromised. The previous data stimulated our group to try the exogenous administration of DHEA to the pregnant women in

order to develop a dynamic fetoplacental unit function test. Our first clinical report[2] clearly demonstrated that the application of a mathematical model of the DHEA to estrogen conversion data resulting in a DHEA to estrogen conversion rate constant was a reliable means of segregating a population of pregnant patients by pregnancy outcome. Although the number of tests and the number of patients was small (19), our results were able to distinguish with significance between normal pregnancies resulting in normally grown infants, high-risk pregnancies resulting in normally grown infants, and high-risk pregnancies resulting in infants showing signs of chronic placental insufficiency.

It was also interesting that no false positive or false negative results were found in that first study. In addition, and possibly because of the small numbers, the DLT could not distinguish between high-risk pregnancies resulting in chronically distressed infants, and those who, while normally grown, developed signs of acute fetal distress during labor. This lack of discrimination may be interpreted as reflecting different degrees of placental sufficiency.

The study of additional patients using the same protocol has again demonstrated that most patients (17 out of 19) who were delivered of normal infants (Groups A and D) had DHEA-to-estrogen conversion rate constants greater than 2.9×10^{-3}.

In contrast, the majority of patients (15 of 17) with compromised fetuses (Groups B and C) showed conversion rate constants of less than 2.9×10^{-3}. Fig. 2 graphically demonstrates the differences in DHEA to estrogen conversion rate constant distributions between these different groups. Table VI shows the significant differences between Groups A and B, Groups B and C, and Groups B and D. In marked contradistinction to these relationships are the intergroup differences in the baseline maternal serum estrogen concentrations. Fig. 1 shows the lack of any consistent intergroup differences in the baseline serum maternal estrogen concentrations and Table IV shows a significant difference in the baseline serum maternal estrogen concentration between groups A and C and Groups B and D. These differences are primarily due to the unusually high baseline serum maternal estrogen concentrations found in Group D, a phenomenon that we do not understand. It should be noted that there was no significant difference in the baseline maternal serum estrogen concentrations between Group A, the normal patients, and Group B, the high-risk patients who delivered infants with signs of chronic placental insufficiency. These data argue against the utilization of maternal serum estrogen concentration as a means of identifying patients at risk of delivering infants with signs of chronic placental insufficiency. This is not to negate the value of serial maternal serum estrogen concentration determinations in predicting pregnancy outcome.

There are seven DLT's in five patients set aside in Table VII that merit further discussion.

Patient G.C.A. of Group D had a markedly abnormal DHEA to estrogen conversion rate constant of 1.2×10^{-3} at 37 weeks' estimated gestational age (EGA). She was considered to be a high-risk obstetric patient because of habitual abortions and a history of toxemia, anemia, and pregnancy associated hypertension with premature labor and delivery on her sole previous successful pregnancy. Approximately one week after the DLT, she was delivered of a 3,000 gram infant with Apgar scores of 9 and 10. There were no signs of fetal distress during labor. Gross examination of the placenta revealed it to be clinically small with multiple calcifications and infarcts. Through an unfortunate oversight the placenta was neither weighed nor examined microscopically. It is of interest that the placental abnormalities (apparently picked up by the DLT) were insufficient to cause either significant growth retardation or fetal distress during labor. This must be considered a false positive DLT.

The other false positive result was obtained in patient M.H.O., who had a DHEA to estrogen conversion rate constant of 1.9×10^{-3} at 38 weeks' EGA. She was delivered of a 2,570 gram infant with Apgar scores of 7 and 9 after an uncomplicated labor and delivery without signs of fetal distress. A high-risk factor of suspected IUGR was noted at the time of the DLT; however, this was not substantiated by Lubchenco chart. We can provide no explanation for this false positive report.

One of the false negative results was obtained from Patient J.R.O. She had a conversion rate constant of 209×10^{-3} at 37 weeks' EGA, well above the normal range. Approximately three weeks later she was delivered of a 3,020 gram infant with Apgar scores of 8 and 10, showing alternating fetal bradycardia and tachycardia during labor. While it can be surmised that an insult occurred after the DLT, or that the distress in labor was not secondary to placental dysfunction, this must be considered a false negative test.

J.P.E was the second patient with a false negative test, but only if the strictest criteria are used. At 33½ weeks' EGA, with a cessation of fundal height growth for 6 weeks, she had a conversion rate constant of 986×10^{-3}, consistent with the group that were delivered of normally grown, nondistressed infants (Group D). Hence, this must be considered a definite false negative result. Because of her clinical IUGR she was placed on

strict bed rest for six weeks, in addition to a high-calorie and high-protein diet. She subsequently had a conversion rate constant of 2.8×10^{-3} at 38 weeks' EGA, showing a resumption of clinical fetal growth in the interim. She went on to be delivered of a 3,100 gram infant with Apgar scores of 8 and 9 approximately 1 week later, showing fetal bradycardia during labor. While the second DLT result was appropriate for the outcome, it is troublesome that the conversion rate constant showed such a dramatic fall in the presence of resumed fundal height growth. This result underscores our lack of understanding of both how well the conversion rate constant reflects placental function, and also of what causes intrauterine growth retardation. It is unfortunate that we do not have ultrasonographic documentation of lack of fetal growth in this case, even though the biparietal diameter seems to be the last parameter to change in IUGR when secondary to placental insufficiency.

A most interesting patient is S.C.A., whose conversion rate constant of 0.7×10^{-3} at 32 weeks' EGA was consistent with a noted lack of uterine growth for 5 weeks. A repeat DLT was done 2 weeks later, after strict bed rest and dietary therapy, revealing her conversion rate constant to be 4.9×10^{-3}, apparently reflecting success of the therapy. She later was delivered of a 4,040 gram infant with Apgar scores of 9 and 9 after an uncomplicated labor and delivery.

We now turn our attention to Group E, comprising five DLT's in four patients. These patients were not included in the above statistical analyses as it was impossible to place them in any of the previously described four groups. They are also included in Table VIII.

Patient V.F.R. had a higher than normal conversion rate constant of 36.1×10^{-3} at 35 weeks' EGA. Then at 35½ weeks' EGA she was delivered of a 900 gram infant with Apgar scores of 3 and 3, with multiple congenital abnormalities (bilateral complete cleft lip and palate, microcephaly, multiple ecchymoses). While this case may be looked upon as false negative, there was no evidence of placental insufficiency and her pregnancy outcome can be presumed to be explained by the observed fetal anomalies. Unfortunately, autopsy was refused by the family.

Patient M.W.I. had documented intrauterine fetal death at 36 weeks' gestation. DLT's were done 1 and 2 weeks later and showed essentially normal conversion rate constants of 4.5×10^{-3} and 3.0×10^{-3}, respectively. This reflects both the expected continuation of placental function after fetal death and the fact that the DLT is in no way a test of fetal function. It is difficult to draw a conclusion from the apparently falling conversion rate constant. She was delivered of a 2,460 gram stillborn infant on the day of the last DLT.

Yet another intrauterine fetal death was evaluated in Patient J.A.N., who had documented fetal death at 29 weeks' gestation. Two weeks later the conversion rate constant was found to be 303×10^{-3}. This result differs greatly from that of the previous patient for reasons that we cannot suggest with any firm basis in fact. We hypothesize that in the absence of basal circulating DHEA the ability of the placenta to convert DHEA to estrogen is markedly increased, at least temporarily. Further studies in patients receiving adrenal steroids, and in patients carrying anencephalic infants, may provide a better understanding.

The final DLT in Table VIII was on Patient J.P.U., a nonpregnant woman. Her conversion rate constant was 0.04×10^{-3} on Day 9 of the menstrual cycle. Unknown to us, on the day of testing, she was taking Synthroid, 0.1 mg per day, for uncomplicated hypothyroidism. While the latter fact renders her a less than perfect control subject, there is no reason to suspect that this would alter the results as she was clinically euthyroid.

The DHEA loading test continues to hold promise as a predictor of pregnancy outcome, ostensibly as a placental function test. However, before the DLT can be applied generally and used as a basis for clinical decisions, extensive testing must be done to further evaluate its diagnostic and possible predictive value in a larger number of normal pregnancies, as well as in pregnancies complicated by various maternal disease processes or poor reproductive histories. At present, there are sufficient data to strongly recommend further evaluation of utilization of DHEA to estrogen conversion dynamics in managing high-risk pregnancies.

Further studies in patients like those studied in Group E (experiments of nature) should provide a better understanding of placental DHEA metabolism.

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Relationship of fetal bradycardia to maternal administration of lidocaine in sheep

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The causal relationship between the use of lidocaine and fetal bradycardia and the effect of the drug on maternal and fetal hemodynamics were studied on 13 chronically instrumented pregnant sheep. Lidocaine was infused intravenously to the mother for 60 minutes during arterial lidocaine concentrations were maintained at 2 to 5 μg per milliliter in the mother and at less than 2 μg per milliliter in the fetus. A decrease in uterine blood flow and an increase in uterine vascular resistance and uterine activity occurred immediately following the administration of lidocaine to the ewe. These changes were followed by a transient fetal bradycardia in 12 out of 17 experiments, accompained by a decrease in fetal Pao_2 values. These phenomena were seen in the absence of such predisposing conditions as maternal hypotension and fetal acidosis. It would appear that the mechanism responsible for a transient fetal bradycardia following regional obstetric anesthesia, particularly paracervical block anesthesia, in the initially nonasphyxiated fetus may in part be related to a brief decrease in perfusion of intervillous spaces. The bradycardia can occur at low lidocaine concentrations in both the maternal and fetal blood in a range similar to that observed in clinical practice. (AM. J. OBSTET. GYNECOL. 134:289, 1979.)

THE MECHANISM underlying the transient fetal bradycardia occasionally seen in association with regional anesthesia, particularly paracervical block, in obstetrics has not been clearly understood, The paracervical block–induced fetal bradycardia has been attributed to a direct toxic effect of local anesthetic on the fetal myocardium, caused by drug absorbed from the highly vascular area of injection and transferred to the fetus.[1] This hypothesis was supported by the presence of significant levels of local anesthetics which were found in the fetal blood following paracervical block.[2–4] However, our previous animal studies have shown that high doses of local anesthetics given directly to the healthy fetal guinea pig or lamb are well tolerated.[5, 6] By contrast, when lidocaine was injected into the pregnant ewe, a transient fetal bradycardia was observed in association with a decrease in fetal cardiac output, umbilical blood flow, and uterine blood flow.[7] These changes occurred at relatively low drug concentration in the fetal blood. Recent in vitro studies have shown that high concentrations of local anesthetics have a vasoconstrictive effect on the uterine artery.[8–10] This vasoconstriction may result in a decrease of uteroplacental blood flow, fetal asphyxia, and bradycardia.[8]

In order to elucidate the causal relationship between

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Table I. Mean ± S.E. for acid-base, mean arterial pressure, and heart rate in the mother and fetus prior to and the end of infusion of lidocaine in 17 experiments

	Mother		*Fetus*	
	Preinfusion	*End of infusion*	*Preinfusion*	*End of infusion*
pHa	7.47 ± 0.009	7.49 ± 0.008	7.36 ± 0.010	7.35 ± 0.020
Pa_{CO_2} (mm. Hg)	33 ± 1.9	33 ± 2.8	45 ± 2.9	48 ± 3.2
Base deficit (mEq./L.)	−0.7 ± 1.2	−3.6 ± 2.0	0.6 ± 0.34	−0.2 ± 0.92
Pa_{O_2} (mm. Hg)	91 ± 2.3	89 ± 3.2	23 ± 1.0	22 ± 1.1
MABP (mm. Hg)	94 ± 1.97	96 ± 2.9	52 ± 2.0	52 ± 2.7
Heart rate (beats/min.)	100 ± 5.4	98 ± 4.8	167 ± 4.6	165 ± 4.5

the use of local anesthetics and fetal bradycardia, the effects of lidocaine on maternal and fetal hemodynamics have been studied.

Materials and methods

A total of 17 experiments were performed on 13 pregnant ewes at gestational ages ranging from 121 to 138 days. Initially the ewes were operated upon under spinal anesthesia with tetracaine, supplemented as necessary with thiopental. Catheters were placed in the femoral artery and vein of the ewe. Catheters were also placed in a carotid artery and internal jugular vein of the fetus through a small hysterotomy incision. A catheter was placed into the amniotic cavity through which intrauterine pressure could be measured and the uterus was closed. The estimated loss of amniotic fluid was replaced with an equal volume of normal saline. An electromagnetic blood flow probe (Micron Instruments, Inc., Los Angeles, Calif.) was applied to the main uterine artery of the pregnant horn, a catheter was inserted into a uterine vein, and the abdomen was closed. The catheters and blood flow probe leads were tunneled subcutaneously and placed in a pouch attached to the flank area of the ewe. The catheters were flushed and filled with heparinized saline solution daily. Experiments were performed in these animals from 2 to 18 days after the initial operation. A minimum of 48 hours was allowed to elapse between experiments to assure recovery of mother and fetus prior to the next observation.

During each study, the ewe was restrained in a cart. Arterial blood pressure and heart rate of both mother and fetus, as well as uterine venous and intrauterine pressures and uterine blood flow were measured and recorded continuously. The arterial pulse waves served as input for the cardiotachometer. Uterine vascular resistance was estimated by dividing the measured mean arterial pressure minus the uterine venous pressure by the uterine blood flow. Arterial blood samples were withdrawn simultaneously from mother and fetus prior to and during the experiment. Blood pH, Pco_2, and Po_2 values were measured with the use of Radiometer microelectrodes and a Radiometer gas analyzer. The base deficit was calculated with the use of the Radiometer blood gas calculator. Blood samples were also analyzed for lidocaine concentrations with a gas chromatographic technique.[11]

None of the mothers was in active spontaneous labor 1 to 2 hours prior to the initiation of the experiment. To examine the effect of increased uterine activity on the uterine blood flow and fetal hemodynamics, oxytocin at the rate of 20 to 30 mu per minute was infused intravenously to the mother in six experiments prior to the administration of lidocaine. The infusion was maintained during the entire course of the experiments. Uterine activity was expressed as Montevideo units (MVU).[12] In order to maintain lidocaine levels in the maternal arterial blood between 2 and 5 μg per milliliter and fetal blood between 1 and 2 μg per milliliter, lidocaine was infused into the maternal vein at the rate of 0.3 to 0.4 mg. per kilogram per minute for the initial 15 minutes, then decreased to 0.1 to 0.2 mg per kilogram per minute for the remaining 45 minutes. Observation was continued for an additional 30 minutes after the completion of lidocaine administration.

Comparisons of data between the period prior to infusion and during infusion of lidocaine were made with a paired t test. Correlations were estimated by linear regression curves.

Results

All mothers and fetuses had normal cardiovascular and acid-base state prior to the infusion of lidocaine (Table I).

Lidocaine concentrations in maternal and fetal blood during and after the intravenous infusion of the drug to the mother are depicted in Fig. 1. The drug levels in blood showed no differences between the group of animals which did and did not receive oxytocin, and the groups have therefore been combined. Maternal level of lidocaine reached approximately 4 μg. per milliliter after 5 minutes at the high rate of infusion; this

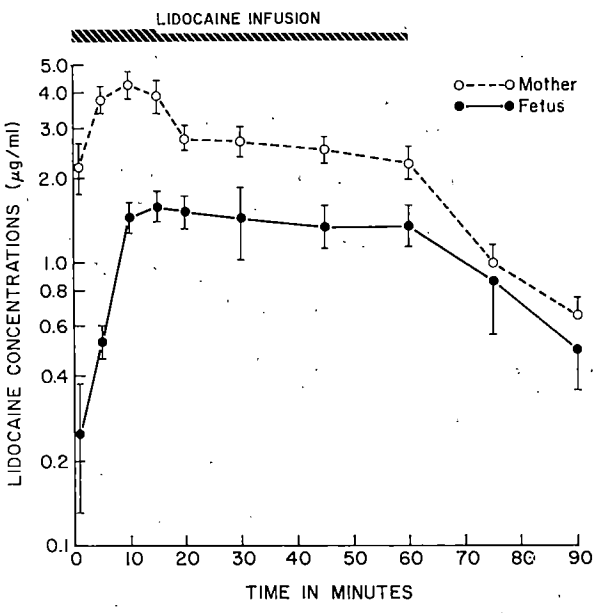


Fig. 1. Mean concentrations and standard error of the mean for lidocaine in arterial blood of the mother and fetus during and after intravenous infusion of lidocaine to the pregnant ewe. Lidocaine was infused at a rate of 0.3 to 0.4 mg. per kilogram per minute for 15 minutes, followed by a reduced rate of 0.1 to 0.2 mg. per kilogram per minute for 45 minutes in 17 experiments.

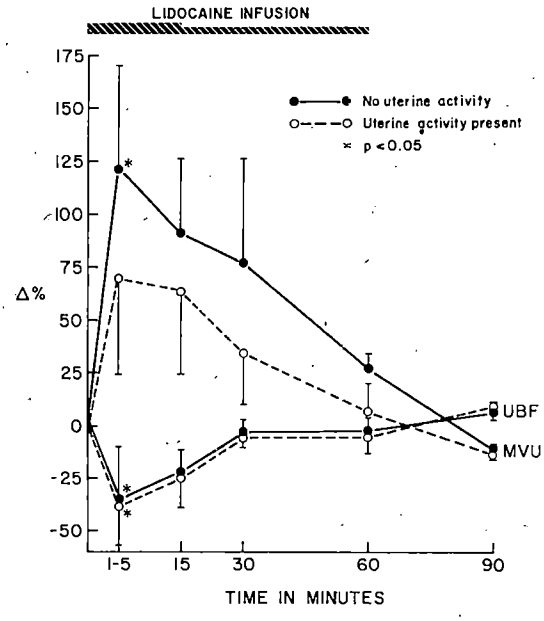


Fig. 2. Mean (S.E.) proportional changes in uterine activity *(MVU)* and uterine blood flow *(UBF)* during and after intravenous infusion of lidocaine to the pregnant ewe. Solid circles indicate animals exhibiting no uterine activity prior to lidocaine administration (N = 11); open circles represent animals in which uterine activity (oxytocin induced) was present before the start of the experiment (N = 6).

level remained steady until the rate was decreased. Following the decrease of the infusion rate, the drug concentration in the maternal blood remained between 2 and 3 μg per milliliter. The initial high rate of infusion brought the lidocaine concentration in the fetal blood up to a plateau of 1.4 to 1.6 μg per milliliter within 10 minutes. The levels remained between 1 and 2 μg per milliliter throughout the infusion.

The infusion of oxytocin in the maternal vein induced uterine contractions with a mean of 160 ± 58 (S.E.) MVU prior to the administration of lidocaine. This was accompanied by a 30 per cent decrease in uterine blood flow when compared to the preoxytocin value of 436 ± 45 ml. per minute. Uterine vascular resistance increased slightly from 0.399 ± 0.0156 to 1.007 ± 0.0381 mm. Hg per milliliter per minute. Prior to giving lidocaine an average of 30 units of oxytocin by infusion was necessary to establish a regular uterine contraction pattern in which the intra-amniotic pressure returned to nearly baseline tone during each contraction.

Proportional changes in uterine activity and uterine blood flow following the infusion of lidocaine are seen in Fig. 2. In 11 experiments where uterine activity was not augmented by oxytocin, the prelidocaine value of uterine blood flow was 392 ± 33 ml. per minute and uterine vascular resistance, 0.255 ± 0.0217 mm. Hg per milliliter per minute. A 122 ± 48 per cent ($P < 0.05$) increase in MVU, with a corresponding decrease of 35 ± 23 per cent ($P < 0.05$) uterine blood flow occurred immediately following the initiation of the infusion of lidocaine. The pattern of uterine contraction was rather tetanic; the resting tone remained elevated during the interval between uterine contractions. Uterine vascular resistance also increased significantly to 2.391 ± 0.892 mm. Hg per milliliter per minute. All six experiments receiving oxytocin prior to lidocaine infusion had an increase in MVU (69 ± 44 per cent) and decrease in uterine blood flow (39 ± 17 per cent) ($P < 0.05$), from the prelidocaine levels. Increase in MVU in this group was not statistically significant. The changes in MVU, uterine blood flow, and uterine vascular resistance were most profound during the first 10 minutes, with the subsequent return toward the preinfusion values, even though the infusion was continued for an additional 50 minutes.

Prelidocaine values of heart rate and arterial pressure in the mothers with or without induced uterine activity were similar. The effect of oxytocin-induced uterine contractions on the fetus was minimal; the heart rate tended to decrease from the preoxytocin level of 171 ± 6.0 to 165 ± 3.4 beats per minute prior to the infusion of lidocaine, but the change was not statistically significant. Initial fetal pHa and Pa_{O_2} were 7.36 ± 0.01 and 24 ± 1.0 mm. hg without oxytocin and 7.36 ± 0.02 and 22 ± 0.8 mm. Hg with oxytocin, re-

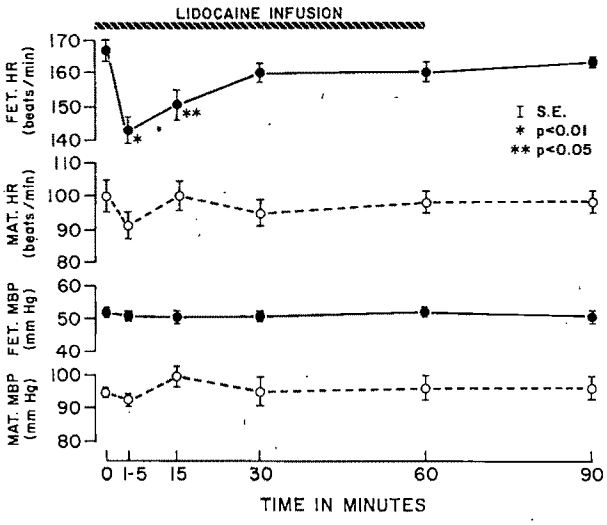


Fig. 3. Changes in the fetal and maternal heart rate and fetal and maternal mean arterial pressure during and after the infusion of lidocaine to the mother. Values are mean ± S.E.; n = 17.

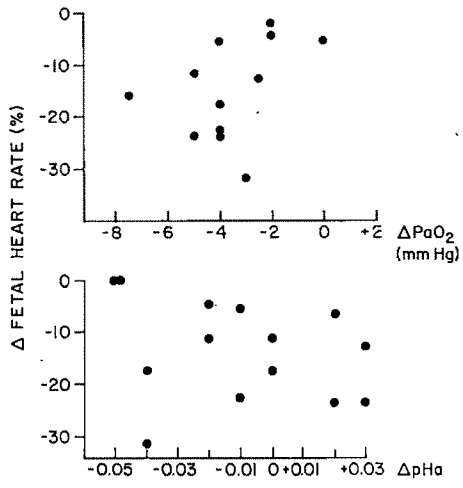


Fig. 4. Relationships between the degree of fetal bradycardia and change in fetal Pa_{O_2} or pHa.

spectively. Therefore all values were combined, regardless of presence or obsence of uterine contractions. Changes in fetal and maternal heart rate and fetal and maternal arterial pressure during and after completion of lidocaine infusion to the mother in 17 experiments are seen in Fig. 3. A significant but transient decrease in fetal heart rate occurred in 12 out of 17 experiments from the preinfusion value of 167 ± 5.7 to 142 ± 4.4 beats per minute ($P < 0.01$), beginning with the first 5 minutes of the infusion and lasting for 15 minutes. In the remaining five, heart rate either did not change or increased slightly. There was no significant change in fetal arterial pressure. Maternal heart rate and blood pressure remained essentially unchanged during the infusion of lidocaine. Blood samples obtained when fetal bradycardia was maximal (during the first 15 minutes) revealed a decreased Pa_{O_2} in all but one of the fetuses (Fig. 4), from a mean preinfusion value of 23 ± 1.0 to 19 ± 1.2 mm. Hg ($P < 0.01$). However, no correlation between the degree of bradycardia and decrease in Pa_{O_2} was found, the correlation coefficient being 0.209; the normal distribution of decreased fetal heart rate and Pa_{O_2} were statistically indistinguishable. The decreased Pa_{O_2} values were only transient; recovery had occurred by the time the next sample was obtained, 5 to 15 minutes after an episode of bradycardia. Pa_{O_2} values remained unchanged in five fetuses in which the heart rate did not change during lidocaine infusion. There was no distinct correlation between fetal bradycardia and changes in fetal pHa (Fig. 4). Fetal Pa_{CO_2} and base deficit values also did not change during bradycardia. The acid-base state of mother as well as fetus remained essentially unchanged throughout the entire observation period (Table I).

A typical recording of the mean uterine blood flow, the intra-amniotic pressure, the heart rate and arterial pressure of the fetus, and those of the mother is presented in Fig. 5. This ewe received the infusion of lidocaine at the initial rate of 0.3 mg. per kilogram per minute for 15 minutes, followed by 0.1 mg. per kilogram per minute. The preinfusion value of the fetal pHa was 7.40; Pa_{CO_2}, 36 mm. Hg; base deficit, 2.0 mEq. per liter; and Pa_{O_2}, 24 mm. Hg. A transient decrease in uterine blood flow from the preinfusion value of 300 ml. per minute to approximately 40 ml. per minute and a marked increase in uterine vascular resistance from 0.252 to 1.783 mm. Hg per milliliter per minute occurred in 2 to 3 minutes after the infusion had begun. This was followed by an increase in uterine activity, with raised intra-amniotic pressure from the preinfusion value of 7 to an average peak of 25 mm. Hg, and frequency of contraction from 0 to 29 per minute respectively. Initial fetal heart rate was 150 beats per minute, but it began to decrease after 5 to 6 minutes of the infusion and became 140 beats per minute after uterine activity and blood flow had begun to recover following 10 minutes of infusion. However, decreased heart rate did not persist longer than 20 minutes; at 25 minutes it had returned to the initial level. Fetal Pa_{O_2} also fell from 24 to 21 mm. Hg, although it was only transient. Lidocaine concentration in the fetal blood was less than 2 μg per milliliter; in the maternal blood it was less than 5 μg per milliliter throughout the infusion. The effect of lidocaine in the presence of oxytocin-augmented contractions is illustrated in Fig. 6. There was an abrupt and marked reduction in uterine blood flow, from 425 to 60 ml. per minute, and an

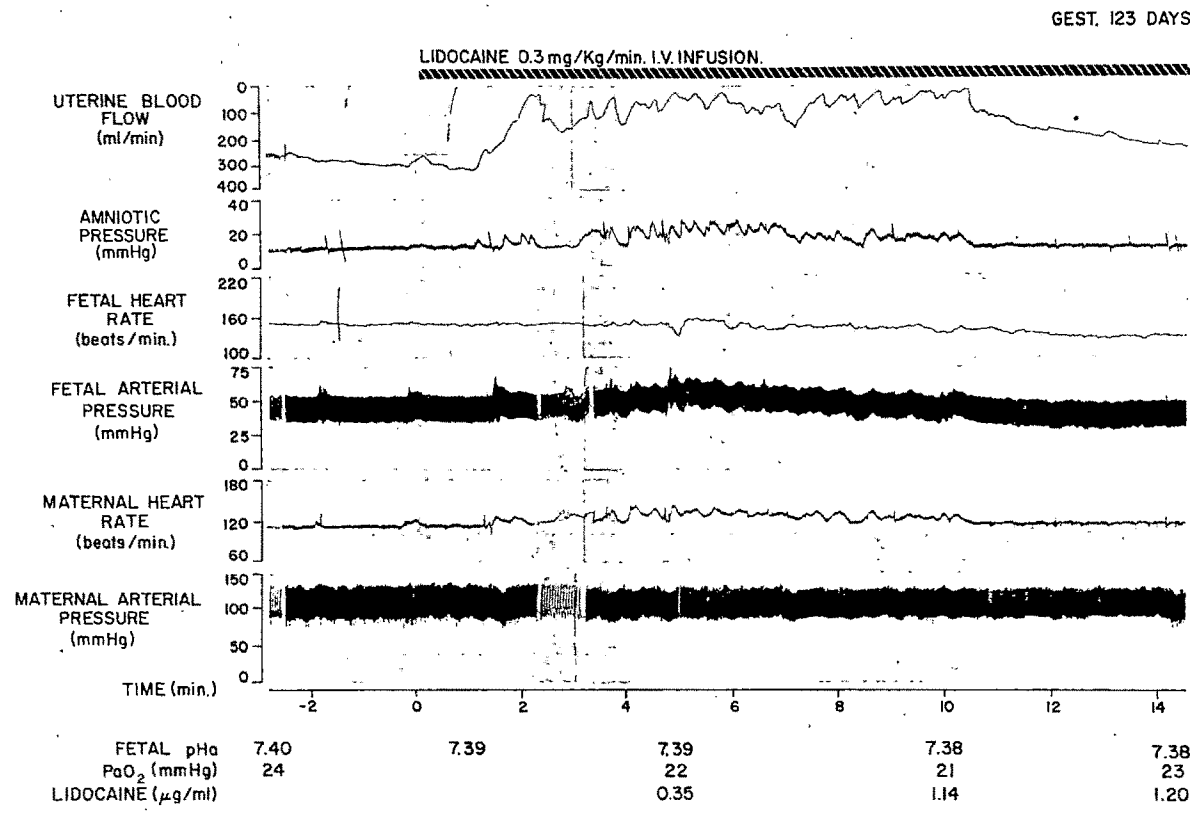


Fig. 5. A typical recording of the mean uterine blood flow, the intra-amniotic pressure, the heart rate and arterial pressure of the fetus, and those of the mother during the infusion of lidocaine at the initial rate of 0.3 mg. per kilogram per minute. Note that the direction of the curve is inverted in the tracing of the uterine blood flow. The upward swing denotes a decrease and a downward swing denotes an increase. The fetal pHa, Pa_{O_2}, and arterial lidocaine levels are shown in the lower space.

increase in vascular resistance from 0.357 to 2.725 mm. Hg per milliliter per minute which corresponded to a rise in uterine activity of approximately 160 MVU from the preinfusion value of 70 MVU. These changes were maintained for 11 minutes, then began to return toward preinfusion values, while lidocaine infusion was continuing. In this experiment the fetal bradycardia occurred earlier (from the initial value of 160 to 120 beats per minute) which was preceded by tachycardia (180 beats per minute). Decreased heart rate was associated with decreased fetal Pa_{O_2} from 24 to 21 mm. Hg. The maternal lidocaine levels ranged between 2.5 and 3.6 μg per milliliter, with fetal levels less than 2 μg per milliliter.

Comment

This study indicates that transient bradycardia, occasionally seen in association with obstetric regional anesthesia, particularly paracervical block, may in part be related to decreased fetal Pa_{O_2} secondary to a reduction in uteroplacental blood flow, an increase in uterine vascular resistance, and an increase in uterine activity. The cause of bradycardia cannot be due only to an elevated drug level in the fetal blood, since the above phenomena can occur at low lidocaine concentrations in both the maternal and fetal blood in a range similar to that observed in clinical practice. The bradycardia can also be induced in the absence of such predisposing conditions as maternal hypotension and fetal acidosis. Therefore, the conclusive etiology of this fetal bradycardia still remains unclear. Following paracervical block, high local anesthetic concentrations have been found in human fetal blood which appear to correlate with the occurrence of fetal acidosis, bradycardia, and subsequent depression at birth,[1–4] which is suggestive of a direct toxic effect of the local anesthetic drug on the human fetal myocardium. Other animal and human studies failed to support this hypothesis. For example, experiments in sheep have shown that the intravenous infusion of lidocaine or etidocaine in the toxic dose to the adult does not produce cardiac depression in the nonasphyxiated fetus,[6, 13] whereas transient decrease in fetal heart rate was observed when lidocaine was infused into the mother in a dose which pro-

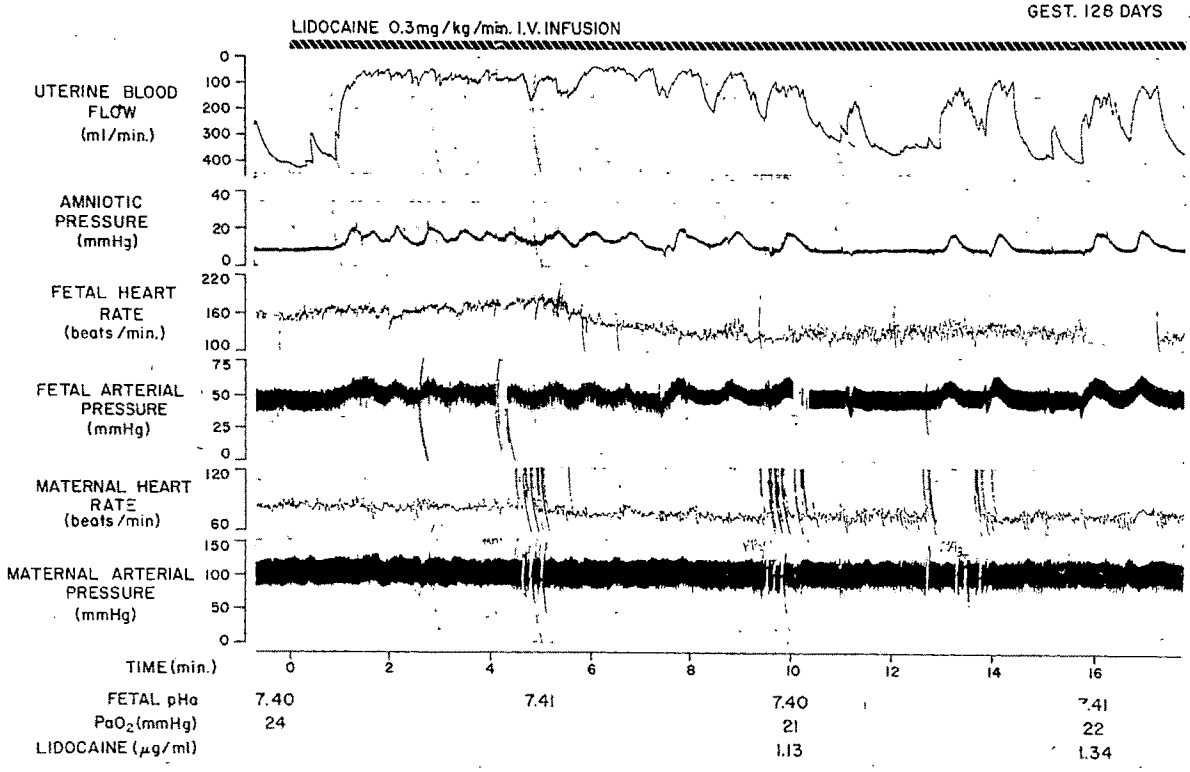


Fig. 6. The effect of lidocaine on the mean uterine blood flow, the intra-amniotic pressure, the heart rate and arterial blood pressure of the fetus, and those of the mother during established regular uterine contractions, induced by oxytocin. Fetal bradycardia occurred earlier and was more profound than those seen in animals not in labor. Note that the direction of the curve is inverted in the tracing of the uterine blood flow. The upward swing denotes a decrease and a downward swing denotes an increase. The fetal pHa, Pa_{O_2}, and arterial lidocaine levels are present in the lower space.

duced a relatively low level of the drug in fetal blood.[7] These studies suggested that a fall in fetal heart rate observed was related more to a decrease in umbilical uterine blood flow than to direct toxic effect of the local anesthetic on the fetal myocardium. Human fetal electrocardiographic studies are also not consistent with a direct toxic effect of anesthetics on the myocardium[14]; the fetal bradycardia observed following paracervical block with mepivacaine was not associated with any signs of conduction defects, whereas the intentional administration of massive doses of mepivacaine directly into anencephalic fetuses showed signs of conduction impairment as seen in studies of adults with toxicity.

In the present study, transient uterine vasoconstriction was observed immediately following the initiation of lidocaine infusion into the maternal vein. This vasoconstrictor effect persisted for approximately 15 minutes, during which time a decrease in fetal Pa_{O_2} value and heart rate was observed. A fall in heart rate could not be related to a direct cardiac effect of lidocaine, since the fall was only transient in nature, while the fetal lidocaine blood concentration remained low at a level of 1 to 2 μg per milliliter. It is more likely that the decrease in Pa_{O_2} value and the fetal heart rate are causally related to the decrease in uterine blood flow, since the fetal Pa_{O_2} and fetal heart rate returned to their normal levels when the uterine blood flow and uterine activity returned toward the preinfusion values. The uterine vasoconstrictor effect of lidocaine has recently been observed by Greiss, Still, and Anderson[8] following the intravascular administration of local anesthetics to pregnant and nonpregnant ewes, the uterine blood flow was reduced. These authors also reported that the reduced uterine blood flow tended to return toward preinfusion values while lidocaine was still being infused. The transient uterine vasoconstrictor action of lidocaine observed in this and other studies may be related to the biphasic vascular effect of local anesthetics reported by other authors. For example, Blair[15] has reported an increase in the myogenic activity of isolated rat portal vein following exposure to low con-

centrations of various local anesthetics. This was followed by a subsequent relaxation of vascular smooth muscle at higher concentrations of local anesthetic. Similar findings have also been reported in man by Jorfeldt and associates.[16] Thus, the uterine vasoconstriction observed immediately following infusion of lidocaine may reflect the stimulatory action of local anesthetics on vascular smooth muscle.

Local anesthetics, when presented to the myometrium in high concentrations, have an oxytocic effect. McGaughey and associates[17] studied the effects of various local anesthetics on isolated pregnant and nonpregnant human myometrium. All the tested drugs increased contraction amplitude and/or baseline tone. Procaine injected into the term human pregnant uterus produced marked hypercontractility.[18] Intravenous injection of lidocaine in patients during labor also increased uterine activity when the drug levels in venous blood ranged between 4 and 7 μg per milliliter.[19] A transient increase in uterine activity accompanied by fetal bradycardia has been reported in 24 out of 92 patients who received paracervical block with mepivacaine.[14] Although both oxytocin and lidocaine increased uterine contractility and decreased uterine blood flow in the present study, the decrease in fetal heart rate and Pa_{O_2} value was significant only during lidocaine administration. Under normal circumstances the oxygen store in the fetal blood and in the intervillous space is more than sufficient to maintain fetal oxygenation during uterine contractions. However, the pattern of contraction produced by lidocaine was more tetanic and persistent, and the increase in uterine vascular resistance was more marked than during oxytocin administration. Therefore, in the presence of lidocaine the interval between uterine contractions was probably not adequate to allow a complete restoration of fetal blood flow and oxygenation prior to the forthcoming contractions. Although decrease in fetal Pa_{O_2} in the human has not been reported during the fetal bradycardia associated with paracervical block, the presence of metabolic acidosis, as indicated by a significant fall in scalp pH and a rise in base deficit,[1, 14] is suggestive of diminished fetal oxygenation. The absence of acidosis in our animals in the presence of a transient fall in Pa_{O_2} is most likely due to the fact that the duration of decreased Pa_{O_2} was not long enough to allow for the development of metabolic acidosis.

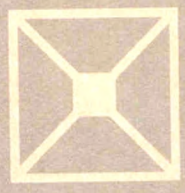
Our results would suggest that the transient fetal bradycardia observed is probably not of great clinical significance in the normal fetus. However, we feel it is important to discuss the possibility of a direct depressant effect of local anesthetics if the fetus is already acidotic and hypoxemic. Since cardiovascular response to local anesthetics has been shown to be more pronounced at low pH and oxygen, the drug levels which are tolerated well by the nonasphyxiated fetus might cause myocardial depression in the asphyxiated fetus.[7] A reduction of umbilical blood flow or cardiac output itself would decrease the clearance of local anesthetic and may accumulate the drug in the fetus. Futhermore, removal of the local anesthetic from the asphyxiated fetus is not as efficient as in the unstressed fetus. Local anesthetics are transferred across the placenta in a nonionized form as weak bases. These drugs will accumulate on the lower pH side of membranes. Therefore, once the drug is transferred to the acidotic fetus, it tends to be trapped in the fetus. Indeed, lidocaine concentrations in the asphyxiated fetal lamb exceeded that in the mother following a single intravenous injection of the drug to the ewe.[7] In contrast, the lidocaine concentration in the nonasphyxiated fetal lamb fell rapidly and paralleled the decrease in drug concentrations in the maternal blood. Brown, Bell, and Alper[20] reported elevated fetal-to-maternal ratios of local anesthetics in four neonates with a low pH in the umbilical venous blood whose mothers received epidural anesthesia with lidocaine or mepivacaine. Thus, the mechanisms responsible for fetal bradycardia following regional obstetric anesthesia in the healthy and depressed fetus may be different.

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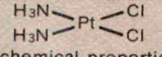
WARNING Platinol (cisplatin) should be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of therapy and complications is possible only when adequate diagnostic and treatment facilities are readily available.

Cumulative renal toxicity associated with Platinol is severe. Other major dose-related toxicities are myelosuppression and nausea and vomiting.

Ototoxicity, which may be more pronounced in children, and is manifested by tinnitus, and/or loss of high frequency hearing and occasionally deafness, is significant.

Anaphylactic-like reactions to Platinol have been reported. Facial edema, bronchoconstriction, tachycardia, and hypotension may occur within minutes of Platinol administration. Epinephrine, corticosteroids, and antihistamines have been effectively employed to alleviate symptoms (see "Warnings" and "Adverse Reactions" sections).

DESCRIPTION Platinol (cisplatin) (cis-diamminedichloroplatinum) is a heavy metal complex containing a central atom of platinum surrounded by two chloride atoms and two ammonia molecules in the cis position. It is a white lyophilized powder with the molecular formula $Pt\,Cl_2H_6N_2$, and a molecular weight of 300.1. It is soluble in water or saline at 1 mg/ml and in dimethylformamide at 24 mg/ml. It has a melting point of 207°C.



ACTION Platinol has biochemical properties similar to that of bifunctional alkylating agents producing interstrand and intrastrand crosslinks in DNA. It is apparently cell-cycle non-specific. Following a single I.V. dose, Platinol concentrates in liver, kidneys and large and small intestines in animals and humans. Platinol apparently has poor penetration into the CNS.

Plasma levels of radioactivity decay in a biphasic manner after an I.V. bolus dose of radioactive Platinol to patients. The initial plasma half-life is 25 to 49 minutes, and the post-distribution plasma half-life is 58 to 73 hours. During the post-distribution phase, greater than 90% of the radioactivity in the blood is protein bound. Platinol is excreted primarily in the urine. However, urinary excretion is incomplete with only 27 to 43% of the radioactivity being excreted within the first 5 days post-dose in human beings. There are insufficient data to determine whether biliary or intestinal excretion occurs.

INDICATIONS Platinol is indicated as palliative therapy to be employed as follows:

Metastatic Testicular Tumors—in established combination therapy with other approved chemotherapeutic agents in patients with metastatic testicular tumors who have already received appropriate surgical and/or radiotherapeutic procedures. An established combination therapy consists of Platinol, Blenoxane (Bleomycin Sulfate) and Velban (Vinblastine Sulfate).

Metastatic Ovarian Tumors—in established combination therapy with other approved chemotherapeutic agents in patients with metastatic ovarian tumors who have already received appropriate surgical and/or radiotherapeutic procedures. An established combination consists of Platinol and Adriamycin (Doxorubicin Hydrochloride). Platinol, as a single agent, is indicated as secondary therapy in patients with metastatic ovarian tumors refractory to standard chemotherapy who have not previously received Platinol therapy.

CONTRAINDICATIONS Platinol is contraindicated in patients with preexisting renal impairment. Platinol should not be employed in myelosuppressed patients, or patients with hearing impairment.

Platinol is contraindicated in patients with a history of allergic reactions to Platinol or other platinum-containing compounds.

WARNINGS Platinol produces cumulative nephrotoxicity. The serum creatinine, BUN, and creatinine clearance should be measured prior to initiating therapy, and prior to each subsequent course. At the recommended dosage, Platinol should not be given more frequently than once every 3 to 4 weeks (see "Adverse Reactions").

Anaphylactic-like reactions to Platinol have been reported. These reactions have occurred within minutes of administration to patients with prior exposure to Platinol, and have been alleviated by administration of epinephrine, corticosteroids and antihistamines.

Since ototoxicity or Platinol is cumulative, audiometric testing should be performed prior to initiating therapy and prior to each subsequent dose of drug (see "Adverse Reactions").

Safe use in human pregnancy has not been established. Platinol is mutagenic in bacteria and produces chromosome aberrations in animal cells in tissue culture. In mice Platinol is teratogenic and embryotoxic.

Platinol has not been studied for its carcinogenic potential but compounds with similar mechanisms of action and mutagenicity have been reported to be carcinogenic.

PRECAUTIONS Peripheral blood counts should be monitored weekly. Liver function should be monitored periodically. Neurologic examination should also be performed regularly (see "Adverse Reactions").

ADVERSE REACTIONS **Nephrotoxicity** Dose-related and cumulative renal insufficiency is the major dose-limiting toxicity of Platinol. Renal toxicity has been noted in 28 to 36% of patients treated with a single dose of 50 mg/M^2. It is first noted during the second week after a dose and is manifested by elevations in BUN and creatinine, serum uric acid and/or a decrease in creatinine clearance. **Renal toxicity becomes more prolonged and severe with repeated courses of the drug. Renal function must return to normal before another dose of Platinol can be given.**

Impairment of renal function has been associated with renal tubular damage. The administration of Platinol using a 6- to 8-hour infusion with intravenous hydration, and mannitol has been used to reduce nephrotoxicity. However, renal toxicity still can occur after utilization of these procedures.

Ototoxicity Ototoxicity has been observed in up to 31% of patients treated with a single dose of Platinol 50 mg/M^2, and is manifested by tinnitus and/or hearing loss in the high frequency range (4,000 to 8,000 Hz). Decreased ability to hear normal conversational tones may occur occasionally. Ototoxic effects may be more severe in children receiving Platinol. Hearing loss can be unilateral or bilateral and tends to become more frequent and severe with repeated doses. It is unclear whether Platinol-induced ototoxicity is reversible. Careful monitoring of audiometry should be performed prior to initiation of therapy and prior to subsequent doses of Platinol.

Hematologic Myelosuppression occurs in 25 to 30% of patients treated with Platinol. The nadirs in circulating platelets and leukocytes occur between day 18 to 23 (range 7.5 to 45) with most patients recovering by day 39 (range 13 to 62). Leukopenia and thrombocytopenia are more pronounced at higher doses (>50 mg/M^2). Anemia (decrease of >2 g hemoglobin/100 ml) occurs at approximately the same frequency and with the same timing as leukopenia and thrombocytopenia.

Gastrointestinal Marked nausea and vomiting occur in almost all patients treated with Platinol, and are occasionally so severe that the drug must be discontinued. Nausea and vomiting usually begin within one to four hours after treatment and last up to 24 hours. Various degrees of nausea and anorexia may persist for up to one week after treatment.

OTHER TOXICITIES **Hyperuricemia** Hyperuricemia has been reported to occur at approximately the same frequency as the increases in BUN and serum creatinine. It is more pronounced after doses greater than 50 mg/M^2, and peak levels of uric acid generally occur between 3 to 5 days after the dose. Allopurinol therapy for hyperuricemia effectively reduces uric acid levels.

Neurotoxicity Neurotoxicity, usually characterized by peripheral neuropathies, has occurred in some patients. Loss of taste and seizures have also been reported. Neuropathies resulting from Platinol treatment may occur after prolonged therapy (4 to 7 months); however, neurologic symptoms have been reported to occur after a single dose.

Platinol therapy should be discontinued when the symptoms are first observed. Preliminary evidence suggests peripheral neuropathy may be irreversible in some patients.

Anaphylactic-like Reactions Anaphylactic-like reactions have been occasionally reported in patients previously exposed to Platinol. The reactions consist of facial edema, wheezing, tachycardia and hypotension within a few minutes of drug administration. Reactions may be controlled by intravenous epinephrine, corticosteroids or antihistamines. Patients receiving Platinol should be observed carefully for possible anaphylactic-like reactions and supportive equipment and medication should be available to treat such a complication.

Other toxicities reported to occur infrequently are cardiac abnormalities, anorexia and elevated SGOT.

DOSAGE AND ADMINISTRATION **Metastatic Testicular Tumors**—An effective combination for the treatment of patients with metastatic testicular carcinomas includes Platinol, Blenoxane (Bleomycin Sulfate) and Velban (Vinblastine Sulfate). Remission induction therapy consists of Platinol, Blenoxane (Bleomycin Sulfate) and Velban (Vinblastine Sulfate) in the following doses:

PLATINOL—20 mg/M^2 I.V. daily for 5 days (days 1-5) every three weeks for three courses.

BLENOXANE® (Bleomycin Sulfate)—30 units I.V. weekly (Day 2 of each week) for 12 consecutive doses.

VELBAN® (Vinblastine Sulfate)—0.15 to 0.2 mg/kg I.V. twice weekly (Days 1 and 2) every three weeks for four courses (a total of eight doses).

Maintenance therapy for patients who respond to the above regimen consists of Velban (Vinblastine Sulfate) 0.3 mg/kg I.V. every 4 weeks for a total of 2 years.

For directions for the administration of Blenoxane (Bleomycin Sulfate) and Velban (Vinblastine Sulfate), refer to their respective package insert.

Metastatic Ovarian Tumors—An effective combination for the treatment of patients with metastatic ovarian tumors includes Platinol and Adriamycin (Doxorubicin Hydrochloride) in the following doses:

PLATINOL—50 mg/M^2 I.V. once every 3 weeks (Day 1).

ADRIAMYCIN™ (Doxorubicin Hydrochloride)—50 mg/M^2 I.V. once every 3 weeks (Day 1).

For directions for the administration of Adriamycin (Doxorubicin Hydrochloride), refer to the Adriamycin (Doxorubicin Hydrochloride) package insert.

In combination therapy, Platinol and Adriamycin (Doxorubicin Hydrochloride) are administered sequentially.

As a single agent, Platinol should be administered at a dose of 100 mg/M^2 I.V. once every 4 weeks.

Pretreatment hydration with 1 to 2 liters of fluid infused for 8 to 12 hours prior to a Platinol dose is recommended. The drug is then diluted in 2 liters of 5% Dextrose in ½ or ⅓N Saline containing 37.5 g of mannitol, and infused over a 6- to 8-hour period. Adequate hydration and urinary output must be maintained during the following 24 hours.

A repeat course of Platinol should not be given until the serum creatinine is below 1.5 mg/100 ml, and/or the BUN is below 25 mg/100 ml. A repeat course should not be given until circulating blood elements are at an acceptable level (platelets ≥100,000/mm^3, WBC ≥4,000/mm^3). Subsequent doses of Platinol should not be given until an audiometric analysis indicates that auditory acuity is within normal limits.

PREPARATION OF INTRAVENOUS SOLUTIONS Dissolve Platinol with 10 ml. of Sterile Water for Injection, U.S.P. Each ml of the resulting solution will contain 1 mg of Platinol.

Reconstitution as recommended results in a clear, colorless solution.

The reconstituted solution should be used intravenously only and should be administered by I.V. infusion over a 6- to 8-hour period. (See Dosage and Administration).

STABILITY Unopened vials of the dry powder must be stored in a refrigerator (2°C to 8°C). The recommended storage of unopened vials provides a stable product for 2 years.

The reconstituted solution is stable for 20 hours at room temperature (27°C).

Important Note: Once reconstituted, the solution should be kept at room temperature (27°C). If the reconstituted solution is refrigerated a precipitate will form.

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MATERNAL NUTRITION AND CHILD HEALTH

By **Douglas R. Shanklin,** *Univ. of Chicago, and* **Jay Hodin,** *Society for the Protection of the Unborn Through Nutrition, both of Chicago. Foreword by* **S. L. Manocha.** This monograph brings together and summarizes an enormous body of information that supports the thesis that good quality protein and calorie nutrition with an abundance of salt and other available nutrients lies at the very root of a successful pregnancy. A relationship between nutritional factors and the entire spectrum of reproductive loss is also noted and substantiated.

Sections I through III of this book detail the effect of starvation on reproductive casualty, the effect of nutrition on birth weight, the relationship of low umbilical cord protein level to the development of respiratory distress syndrome, prospective and retrospective studies of effects of maternal nutrition, and the Vanderbilt cooperative study.

The physiological effects of malnutrition in correlation with impaired brain development and placental pathology are covered in Section IV. Also discussed are consequences of sodium deficiency, pathogenesis of metabolic toxemia of late pregnancy, and less direct evidence of pernicious effects of malnutrition.

Sections V through VIII explore the causal relationship between birth weight and prenatal nutrition, the association of mental deficiency with low birth weight and neurological damage and mental deficiency, interracial differences in reproductive causality, and the relation of maternal health to infant health and development. Maternal complications, the significance of prepregnancy weight and weight gain during pregnancy, and the effects of nutrition during infancy and early childhood are included.

Section IX presents a summary and conclusion of the scientific data introduced in this text.

The authors have done an excellent job of collecting and compiling pertinent information on the nutrition of the pregnant woman and its influence on her offspring. Numerous tables and other reference materials will permit this book to be used as a point of departure for further clinical and research studies. Obstetricians will find this volume extremely informative. *'79, 224 pp., 9 il., 68 tables, $14.75*

FEMALE URINARY STRESS INCONTINENCE *edited by* **Edward B. Cantor,** *Cedars-Sinai Medical Center, Los Angeles. Foreword by* **C. Paul Hodgkinson.** *(16 Contributors)* Sixteen urologists and gynecologists of international repute have collaborated to produce this comprehensive look at female urinary stress incontinence. Their contributions cover the latest theoretical and practical aspects of neuroanatomy, physiology and urodynamics. Chapters discuss the supports of the urethra, the role of the pubourethral ligaments in maintaining urinary continence, the detrusor dyssynergia syndrome, the electronic vaginal pessary, and the sling operation. Also presented is an optimal method of classifying and describing the exact degree of the anatomical defects involved in inadequate pelvic supports. *'79, 360 pp., 175 il., 19 tables, $27.50*

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COLPOSCOPY: A Scientific and Practical Approach to the Cervix and Vagina in Health and Disease (2nd Ed.) *by* **Malcolm Coppleson,** *King George V Memorial Hospital, Sydney, Australia;* **Ellis Pixley,** *King Edward Memorial Hospital, Perth, Australia; and* **Bevan Reid,** *Univ. of Sydney, Sydney, Australia. (5 Contributors)* This completely rewritten and updated Second Edition continues to offer the reader an unsurpassed account of all aspects of the practice of colposcopy. Discussions focus on the topography of the cervical epithelia, the natural history of squamous metaplasia and the transformation zone, and tissue basis of colposcopic appearances. *'78, 512 pp. (6 3/4 x 9 3/4), 306 il. (1 in color), 11 tables, $36.50*

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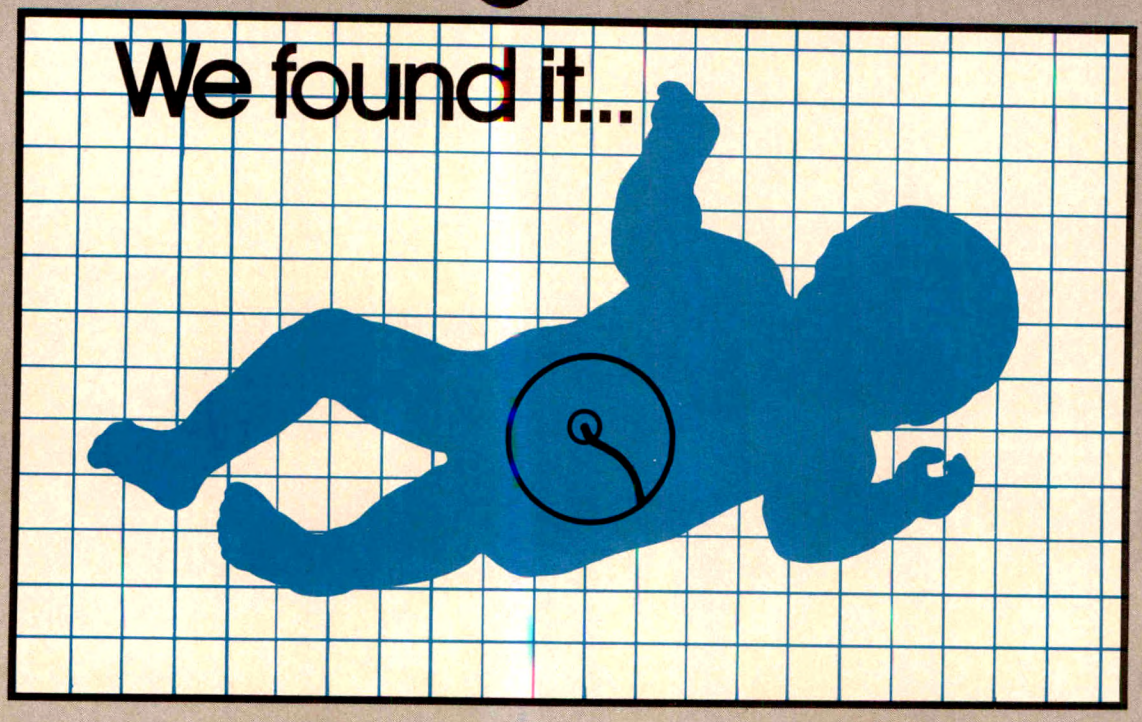
PHYSICIANS' HANDBOOK OF NUTRITIONAL SCIENCE (4th Ptg.) *by* **Roger J. Williams,** *Univ. of Texas, Austin. Foreword by* **I. Newton Kugelmass.** The author provides a straightforward, readable account of the crucial meaning of nutrition and its importance in medical practice. In the few instances where he speculates or voices his opinion, the difference between fact and opinion is made evident. The main purpose of this text is to present facts from which the physician can draw his or her own deductions. Some of the topics considered are prenatal nutrition, internal nutrition and biochemical individuality. *'78, 128 pp., $11.50*

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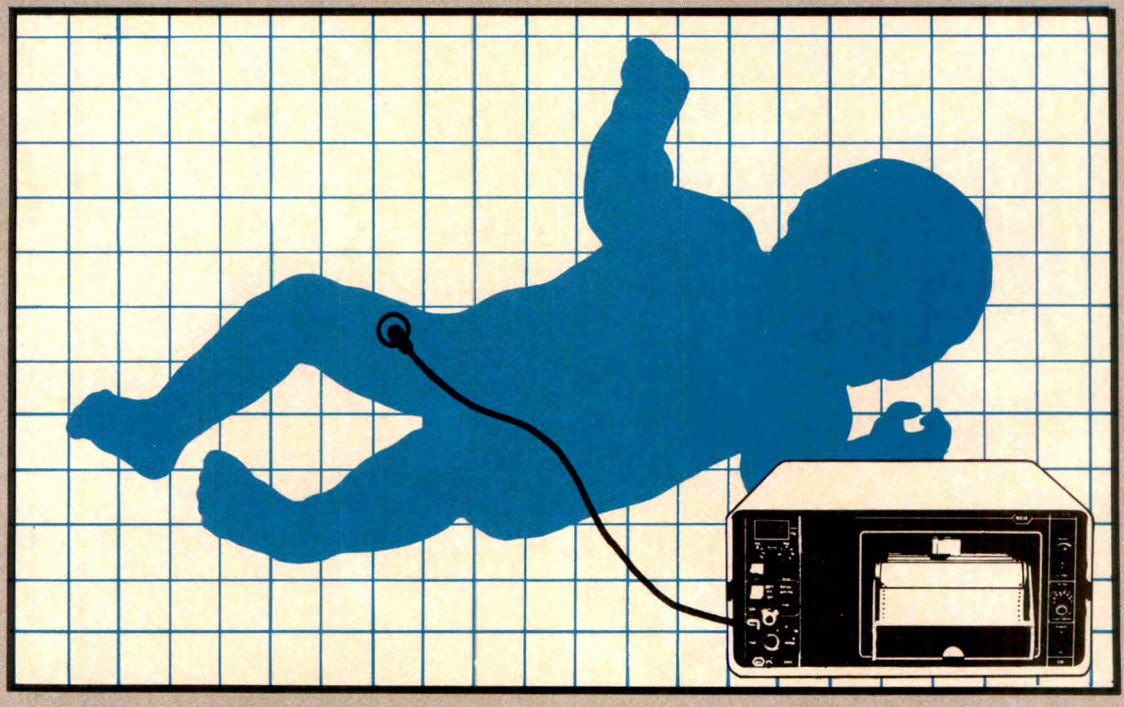
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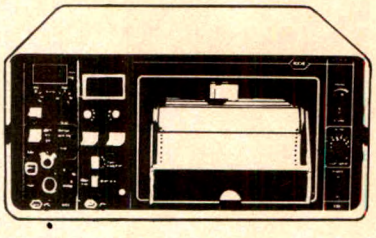
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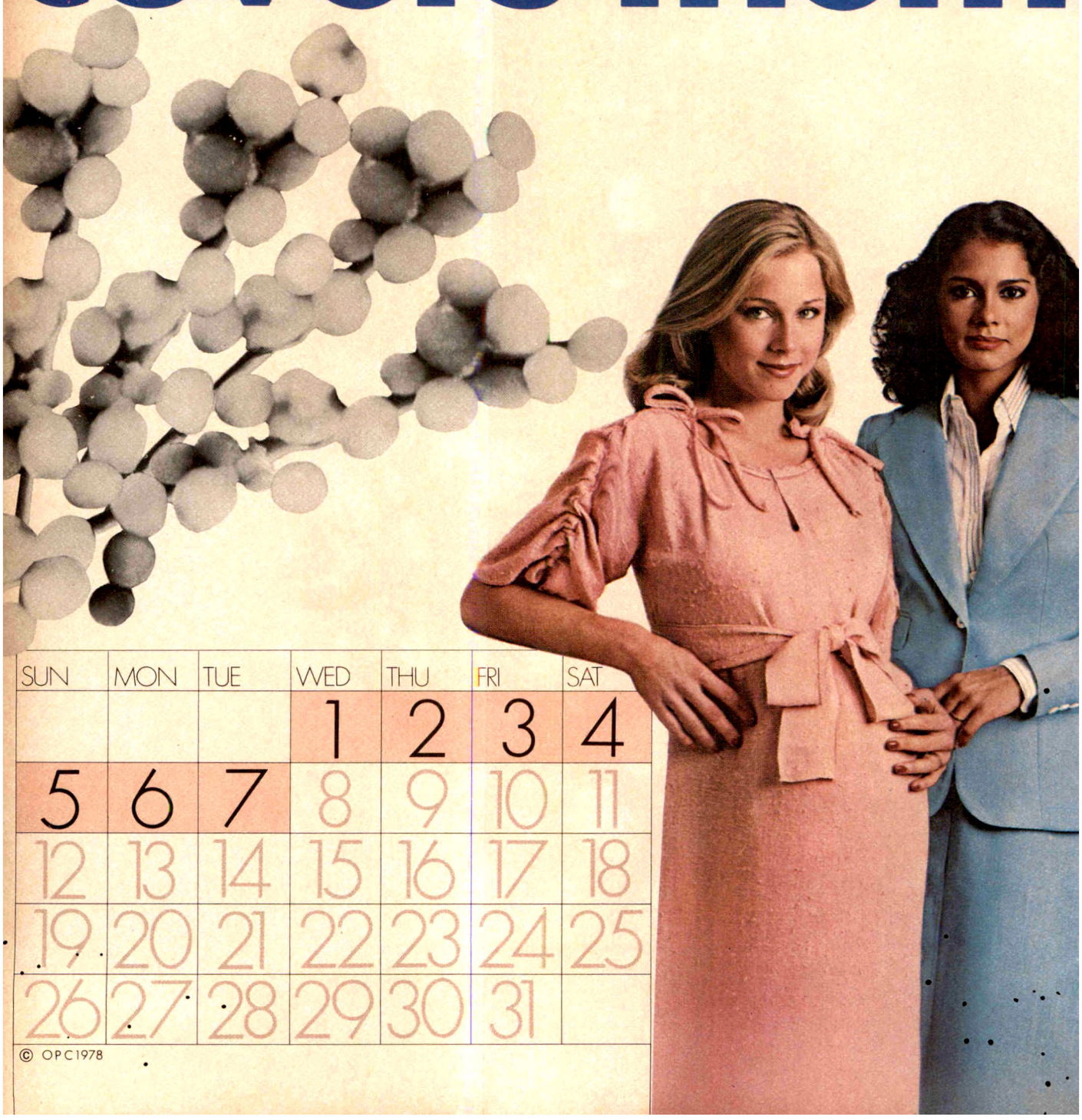
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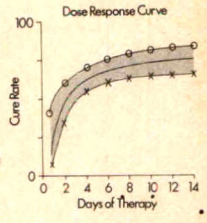
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†MONISTAT 7 Vaginal Cream may be used in second and third trimester patients. However, in first trimester patients, it should only be used when the physician considers it essential to the patient's welfare. See Precautions in Prescribing Information.

Description MONISTAT 7 Vaginal Cream (miconazole nitrate 2%) is a water-miscible, white cream containing as the active ingredient, 2% miconazole nitrate, 1-[2, 4-dichloro-β-(2, 4-dichlorobenzyloxy) phenethyl] imidazole nitrate.
Actions MONISTAT 7 Vaginal Cream exhibits fungicidal activity *in vitro* against species of the genus *Candida*. The pharmacologic mode of action is unknown.
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MONISTAT 7 is effective in both pregnant and non-pregnant women, as well as in women taking oral contraceptives. (See **Precautions**.)
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Precautions General: Discontinue drug if sensitization or irritation is reported during use. Laboratory Tests: If there is a lack of response to MONISTAT 7, appropriate microbiological studies should be repeated to confirm the diagnosis and rule out other pathogens.
Pregnancy: Since MONISTAT is absorbed in small amounts from the human vagina, it should be used in the first trimester of pregnancy only when the physician considers it essential to the welfare of the patient. Clinical studies, during which MONISTAT was used for 14 days, included 209 pregnant patients. Follow-up reports now available in 117 of these patients reveal no adverse effects or complications attributable to MONISTAT therapy in infants born to these women.
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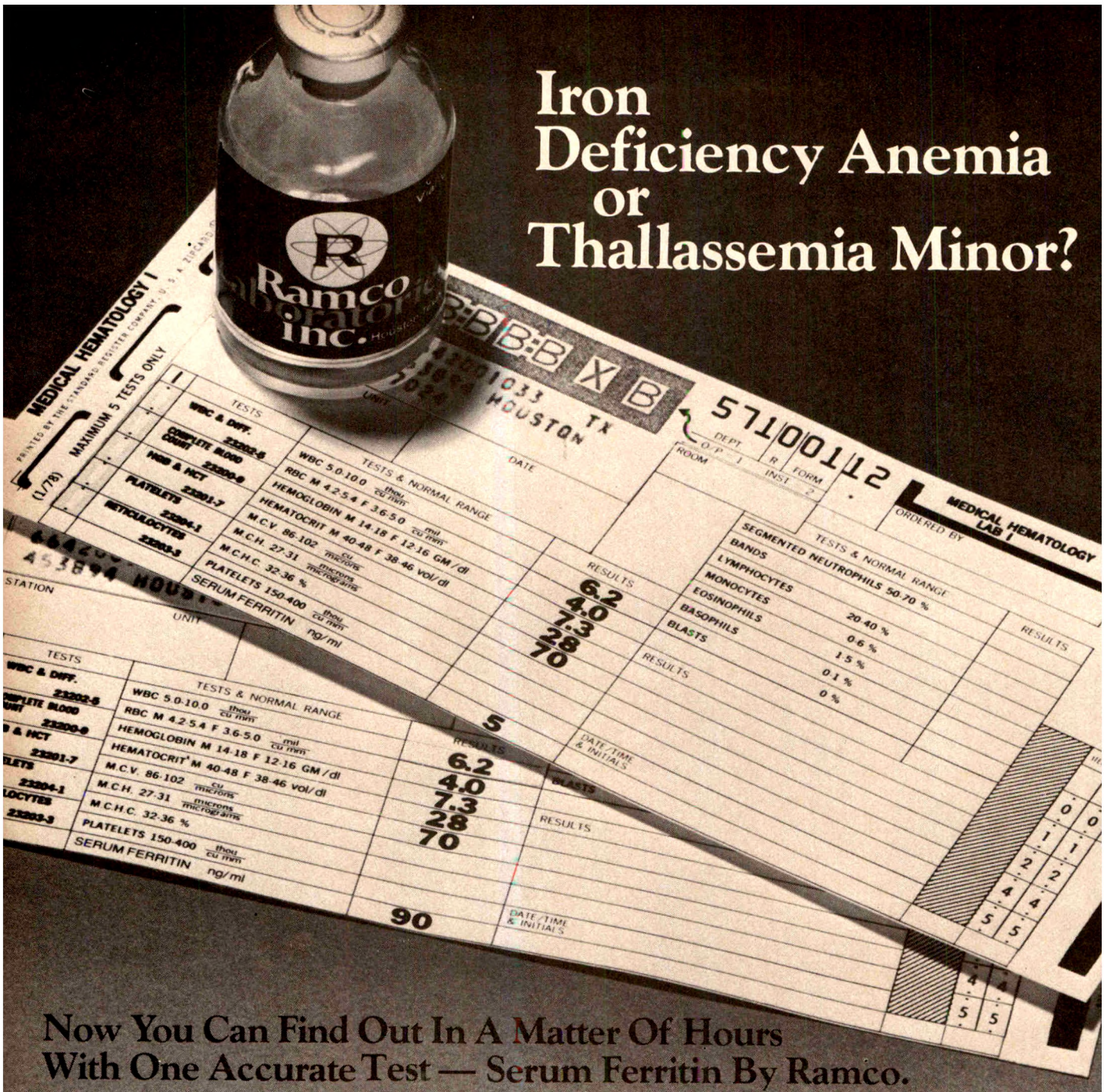
Dosage and administration One applicatorful is administered intravaginally once daily at bedtime for seven days. Course of therapy may be repeated after other pathogens have been ruled out by appropriate smears and cultures.
Supplied MONISTAT 7 Vaginal Cream is available in 1.66 oz. (47 g) tubes with ORTHO* Measured-Dose Applicator. MONISTAT Cream (miconazole nitrate 2%) is a development of Ortho Pharmaceutical Corporation and Janssen Pharmaceutica, Belgium.

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GYNECOLOGY

Studies on the cytodynamics of human endometrial regeneration

III. In vitro short-term incubation historadioautography

ALEX FERENCZY, M.D.
GRACIA BERTRAND, B.Sc.
MORRIS M. GELFAND, M.D., F.R.S.C.(C.)
Montreal, Quebec, Canada

The proliferation kinetics of endometrial regeneration were assessed by tracing nucleoprotein precursor, radiothymidine. Increased isotope uptake occurred by cycle day 3 and was confined to the gland cells of denuded stratum basale (basal layer) and persistent uterine lining, bordering peripheral areas of denudation. This increase resulted in the formation of flattened surface epithelial cells, which initially were devoid of significant deoxyribonucleic acid synthesis. Such alterations are consistent with changes in cells involved in ameboid migration. Maturation of migrating cells was accompanied by a significant rise in labeling indices and replication at cycle days 3 and 4. By cycle day 5, endometrial repair was complete. The findings indicate that, following physiologic loss of stratum functionale, endometrial healing involves both migration and replication of surface cells, which originate from the gland stumps of the residual basal layer and the persistent surface epithelium adjacent to the periphery of denuded endometrium. (AM. J. OBSTET. GYNECOL. 134:297, 1979.)

RECENT ULTRASTRUCTURAL STUDIES[1, 2] on regenerating human endometrium revealed that the total approximate generation time for re-epithelialization of postmenstrual surface is 48 hours (±12 hours), beginning between cycle days 2 and 3 in a normal four-day menstrual period. The mechanism of recovery of the denuded surface is by a simultaneous and progressive epithelial outgrowth from the mouths of basal glands and by ingrowth from the surface epithelium adjacent to the denuded areas, namely from the isthmic and peritubal ostia or cornual regions. Both the basal glands and surface epithelium of peripheral uterine regions remain intact during the menstrual period.

The subsequent development of interanastomoses between converging epithelial proliferations leads ultimately to complete reconstruction of a new surface epithelium by cycle day 5. The studies revealed, furthermore, that the predominant proliferative activity during endometrial regeneration is confined to the formation of a new surface epithelium and that the stroma remains relatively inactive until surface re-epithelialization is completed. Since endometrial mor-

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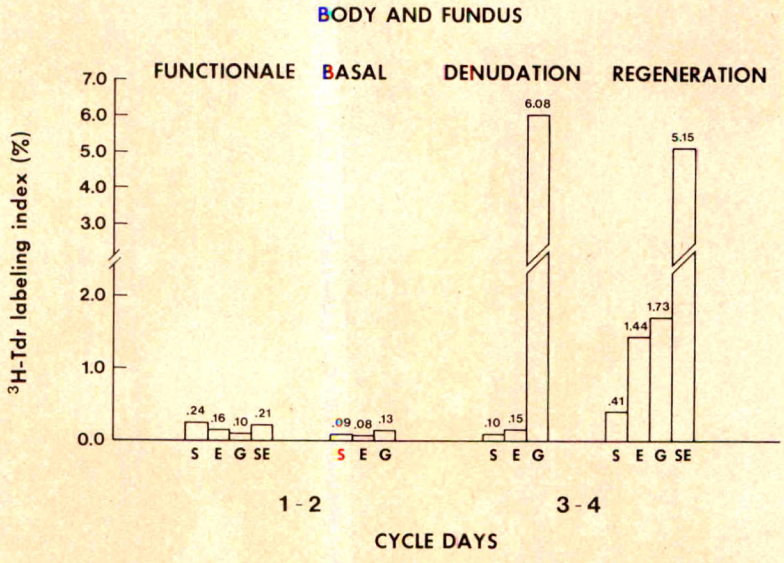


Fig. 1. Zonal and cellular distribution of mean intensity of tritiated thymidine *(^{3}H-Tdr)* labeling of endometrial mucosa during periods of menstrual breakdown and regeneration. Note negligible LI on cycle days 1 and 2 and sharp increase in the residual basal glands and newly formed surface epithelium on cycle days 3 and 4. *S*, stromal fibroblasts; *E*, capillary endothelium; *G*, glandular epithelium; *SE*, surface epithelium.

Table I. Mean tritiated thymidine labeling of resurfacing epithelium in relation to differentiation, growth pattern, and repopulation of denuded basal layer during periods of regeneration

Predominant type of differentiation of resurfacing cells	*Cellular growth pattern*	*LI (%)*	*Estimated re-epithelialization of denuded basal layer*	*Cycle day*
Spindle shaped	Migration	0.2	±20	3 ± 6-12 hr.
Cuboid	Replication	7.0	±65	3-4
Columnar	Replication	7.5	±100	4-5

Table II. Mean tritiated thymidine labeling of endometrial mucosa during cycle days 5 to 7, according to anatomic segments, histologic zones, and cellular compartments

	Stratum functionale (% labeling)				*Basal glandular epithelium (% labeling)*
	Stromal fibroblasts	*Vascular endothelium*	*Surface epithelium*	*Glandular epithelium*	
Fundus	9.5	7.1	7.0	15.5	2.8
Body	9.8	6.8	7.5	15.3	3.0
Isthmus	2.0	2.3	6.7	4.5	1.8
Peritubalostia	8.4	7.4	7.2	15.1	2.8

phologic changes known to be associated with estrogenic stimulation occur only following complete surface re-epithelialization coinciding with the increasing plasma and tissue receptor levels for estradiol-17β, we have suggested that endometrial surface regeneration is likely a local reaction to injury, presumably induced by loss of endometrial mucosa, and is not mediated by the ovarian hormones.[1, 2]

Experimentally induced endometrial regeneration in the rabbit resembles the resurfacing human endometrial cells in reference to the time sequence of events and site of origin.[3] In vivo historadiographic studies using radiothymidine demonstrated an increase in nucleic acid synthesis in all of the endometrial compartments, which are involved in the repair of lost tissue. Increase of isotope uptake above control levels occurs between six and 12 hours after injury and progresses until the second postexcision day. By day 3 after injury,

endometrial regeneration is completed coincident with a return of labeling index to baseline levels. A rising labeling index in regenerating endometrium is correlated with a gradual increase in both the mitotic activity and areas being repaired. The increase in deoxyribonucleic acid (DNA) synthesis in the resurfacing cells and cells immediately adjacent to them precedes this increase in the stromal fibroblasts by about 18 hours, indicating that the newly formed surface lining derives from the persistent surface epithelium bordering the denuded areas rather than from stromal fibroblasts.

In this article we report the results obtained by in vitro short-term quantitative historadioautography using tritiated thymidine (^{3}H-labeled thymidine) in human endometrium during the menstrual and postmenstrual periods. We were particularly interested in study of the mechanisms, time sequences, and zonal characteristics of endometrial repair and the relationship of nucleic acid synthesis to endometrial cellular compartments involved in postmenstrual endometrial regeneration.

Material and methods

We studied a total of 21 uteri obtained from normally menstruating* women (aged 27 to 42 years) on cycle days 1 and 2 (six uteri); 3 and 4 (six uteri); and 5 to 7 (nine uteri). The selection of patients, data of recovery of specimens, and processing of specimens are described in detail in a previous communication on the scanning electron microscopic aspects of endometrial regeneration.[1] The uteri were opened along the lateral borders under a tissue culture hood within 5 minutes of obtaining them in the operating room. Using sterile instruments and under the guidance of a dissecting microscope, samples were taken from the body, fundus, peritubal ostia, and isthmus (lower uterine segment) regions. Blocks of endometrium measuring 1 by 1 by 0.2 cm. were excised along with a thin layer of subjacent myometrium and placed in a pool of oxygenated sterile Earle balanced salt solution (BBS)† at pH 7.0 at room temperature. Each block of endometrium was pinned on dental plates and minced into 1 sq. mm. tissue fragments, always preserving proper orientation and the whole thickness of the endometrium from the myometrium to the surface. The explants were collected on lens paper, moistened with a drop of Earle BBS, and placed into Petri dishes containing 5 ml. of Trowell T8.† No radioisotope was added to the control dishes containing medium, whereas those dishes for the experiment received 10 μCi per milliliter of methyl–^{3}H-labeled thymidine (specific activity, 47,000 to 50,000 μCi per millimole).* The Petri dishes containing both the test and control tissues were placed in a plastic box sealed with tape, and a gas mixture of 5 per cent CO_2 and 95 per cent oxygen was passed through a pinhole made in the cover of the box. Both the control and test tissues were incubated at 37° C. for one hour. Following incubation, the explants were washed three times in Earle BBS, fixed in Bouin's solution, dehydrated, and embedded in paraffin. Sections cut at 2.5 μ were prestained with hematoxylin and dipped into liquefied nuclear emulsion Kodak NTB2. The radioautographs were exposed for four days, developed in Kodak D-170 for six minutes, and fixed in Kodak Rapid Fixer.

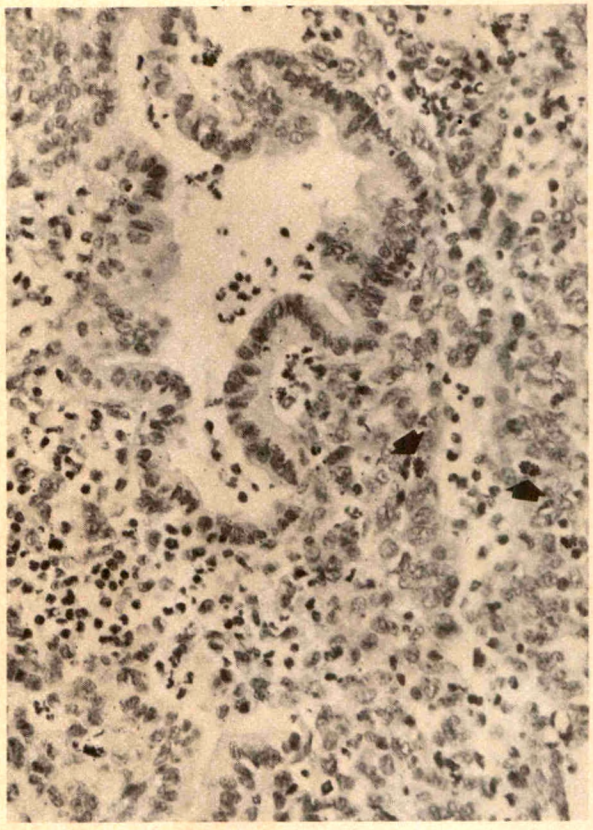


Fig. 2. Radioautograph of glands and predecidua from the lower stratum functionale endometrium from cycle days 1 and 2. Note degenerative features and inconspicuous labeling of predecidual cells (arrows). (Hematoxylin and eosin. Original magnification ×250.)

Interpretation of the radioautographs. Because tritiated thymidine may not label the whole thickness of the tissue fragments, our counts were restricted to the outer third, near the edges of the sections. In this area, grain counts and labeling indices were reproducible.

*The term "menstruation" in this article refers strickly to bleeding from secretory progestational endometrium in association with at least six previous regular ovulatory cycles.

†Gibco.

*Radiochemical Center, Amersham/Searle Corp., Arlington Heights, Illinois.

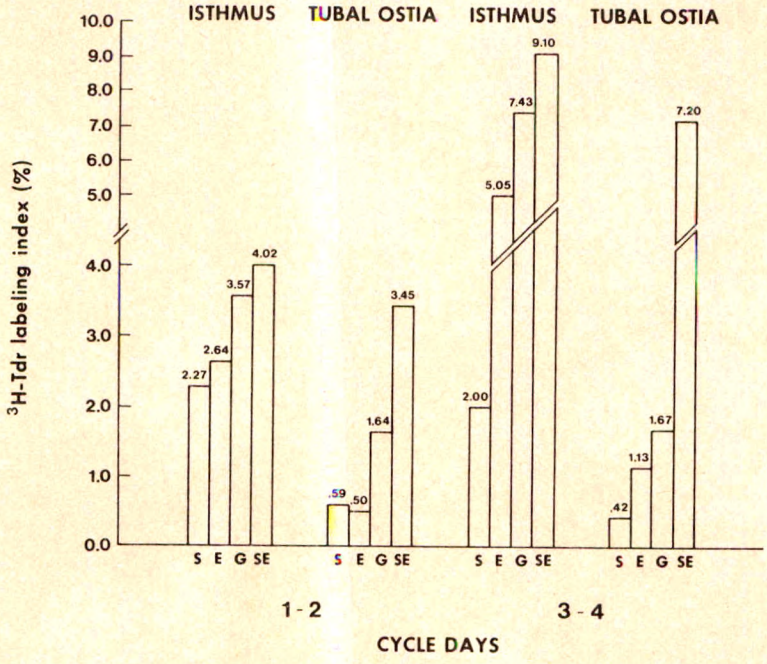


Fig. 3. Zonal and cellular distribution of mean intensity of tritiated thymidine labeling of isthmic and peritubal ostia endometria bordering menstrual endometrium. Note sharp increase in LI on cycle days 3 and 4 coinciding with endometrial regeneration. See Fig. 1 for abbreviations.

Only cells with five or more grains over the nucleus were considered labeled and the percentages of labeled cells were determined by consecutively counting 1,000 to 3,000 cells over: (1) the stratum functionale including the surface epithelium, the glandular epithelium, stromal fibroblasts, and endothelial cells and (2) the basal layer including the regenerating surface epithelium, stromal fibroblasts, and endothelial cells. The labeling index (LI) was then calculated by the following formula:

$$\text{LI (\%)} = \frac{\text{Number of labeled cells} \times 100}{\text{Unlabeled cells}}$$

Because of the limited number of specimens studied and to achieve statistical significance, each count, expressed as a percentage in Figs. 1 and 3 and Tables I and II, represents pooled data from equal areas of three endometria obtained on each cycle day.

Results

There were no appreciable quantitative differences in isotope uptake between the fundus and body regions of the endometrial cavity and thus the findings obtained in these regions will be described as one. The pattern of DNA synthesis was uniform in the various endometrial segments and cellular compartments with a variation of less than ±1.5 per cent.

First- and second-day menstrual endometrium. The distribution of labeling intensity by tritiated thymidine (expressed as a mean) in various tissue components of the endometrium is shown in Fig. 1. In accordance with the massive degeneration of secretory endometrial tissue of the stratum functionale of the fundal and body regions, isotope uptake was negligible (Fig. 2) in both the glandular and surface epithelia with mean LI's of 0.10 and 0.21 per cent, respectively. The predecidual and vascular endothelial cells of menstruating stroma demonstrated similar low levels, 0.24 and 0.16 per cent, respectively. The LI in the basal layer was even lower, with the exception of the glandular apparatus, 0.13 per cent (Fig. 1).

The pattern of DNA synthesis in areas that were not involved in the menstrual breakdown, such as the peripheral isthmic region, remained essentially unchanged (Fig. 3) from that observed during the postmenstrual proliferative or secretory phase of the menstrual cycle (mean LI of isthmus is constant during the menstrual cycle: surface epithelium, 4.7 per cent; glandular epithelium, 3.3 per cent; stromal fibroblasts, 2.2 per cent; and vascular endothelium, 2.0 per cent.[4] On the other hand, in the region of the peritubal ostia, only the surface and glandular epithelia demonstrated an LI unchanged from that observed during the proliferative phase (mean LI's of surface and glandular epithelia of tubal ostia during the proliferative phase are 3.9 and 1.5 per cent, respectively).[4] The adjacent and subjacent stromal tissue, including the predecidua and capillary endothelium, demonstrated degenerative

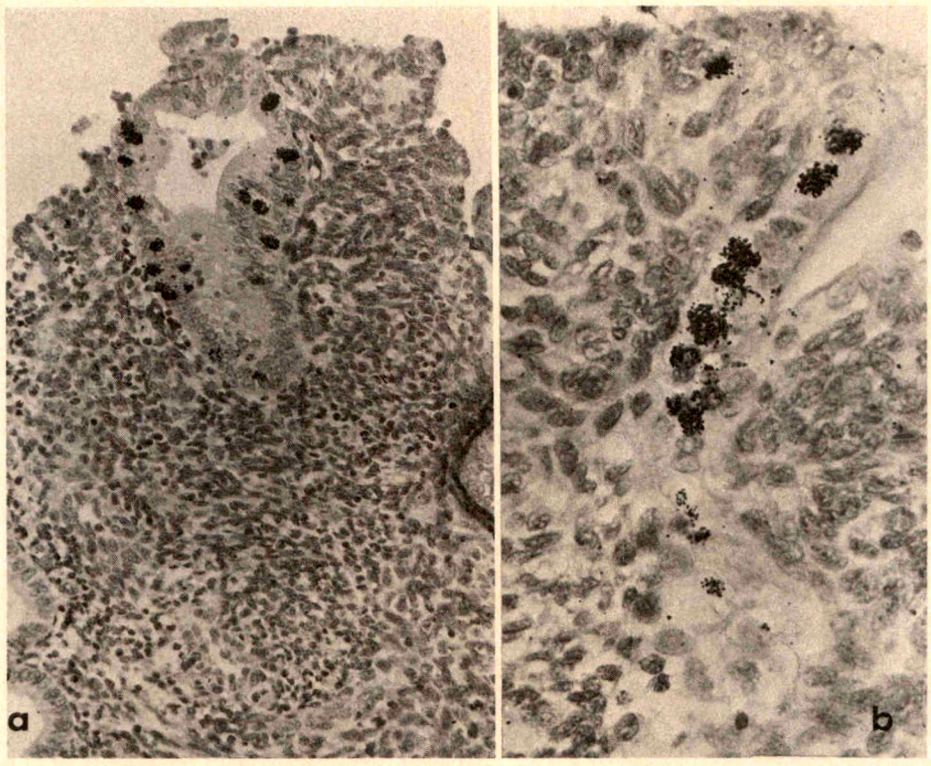


Fig. 4. *(a)* Radioautograph of denuded basal glands of endometrium from cycle days 3 and 4. Note heavy labeling is confined to gland lining cells. (Hematoxylin and eosin. Original magnification, ×250.) *(b)* Higher magnification illustrating concentration of labeled cells at the basal gland neck region. (Hematoxylin and eosin. ×400.)

changes with mean LI values very similar to those in the fundal regions (Fig. 3).

Third- and fourth-day menstrual endometrium. During this period, regeneration rather than degeneration prevailed. In areas where denudation had occurred following desquamation of the degenerated stratum functionale, a dramatic increase in LI (6.08 per cent) was observed in the basal glands (Fig. 1). Isotope uptake was concentrated near the free stumps of glands of the residual basal layer (Fig. 4). In areas of surface re-epithelialization, the LI increased in favor of the newly formed surface epithelial cells, with a mean LI of 5.15 per cent, whereas it decreased sharply in the subjacent gland cells of the zona basale (Figs. 1 and 5). The distribution of radioisotope in the resurfacing and apparently expanding surface epithelial cells followed the same pattern both in the fundus-body and the isthmic and peritubal ostia regions, and was correlated with changes in cell morphology. While tritiated thymidine uptake was neglibible (mean LI, 0.2 per cent) in the earliest, spindle-shaped resurfacing cells, DNA syntheis had increased sharply in the cuboid and columnar cell variety (Fig. 6), with mean LI's of 7.0 and 7.5 per cent, respectively (Table I).

Coinciding with epithelial resurfacing, the underlying stromal fibroblasts and capillary endothelial cells demonstrated approximate fourfold (0.41 per cent) and tenfold (1.44 per cent) increases in DNA syntheis, respectively, as compared to areas of denudation (Fig. 1). Isotope incorporation also increased significantly in areas bordering zones of degeneration, including the isthmic and peritubal ostia regions. However, when values are compared with those of cycle days 1 and 2, the mean LI's of 7.43 per cent for the glandular epithelium and 9.10 per cent for the surface epithelum of the isthmus represent only about twofold increases (Fig. 3) as compared to the more than sixfold increase for the surface epithelial system of the regenerating basal layer of the uterine fundus-body (Fig. 1).

With regard to nuclear DNA synthesis in the peritubal ostia region, only the persistent surface epithelium showed a twofold increase in LI, whereas the glandular epithelium remained unchanged from previous days of the menstrual period (Fig. 3). The stromal fibroblasts in this region as well as in the isthmus demonstrated no significant differences in mean tritiated thymidine uptake when compared to that found in prior regeneration; however, a twofold in-



Fig. 5. Radioautograph of regenerated endometrium on cycle day 4. Resurfacing of denuded basal layer is associated with an increase in labeled surface cells and decrease or absence of isotope uptake in the subjacent basal gland cells. (Hematoxylin and eosin. Magnification ×320.)

crease in LI was observed in the vascular endothelium (Fig. 3).

Endometrium of cycle days 5 to 7. The relative LI's of various layers of the endometrial mucosa and cellular components are listed in Table II. Once epithelial resurfacing has been completed by cycle day 5, a dramatic increase in nuclear DNA synthesis is observed in all the cellular components of the young stratum functionale, with maximum values in the glandular epithelium. There were no significant variations in LI between the body and fundus regions. The sudden increase in LI is accompanied by the appearance of mitotic activity in stromal and endothelial cells as well as in surface and gland lining cells. On the other hand, the elevated LI observed during cycle days 3 and 4 in epithelial lining of the isthmic endometrium and peritubal ostia surface bordering denuded areas, declined sharply (Table II) and almost returned to the level found on first menstrual day (Fig. 1). On cycle days 8 to 10, a further increase in LI and mitotic activity of the stratum functionale endometrium of the body-fundus is observed.[4]

Comment

The results confirm earlier observations[1, 2] that endometrial regeneration begins by cycle day 3 following menstrual tissue necrosis, results in the formation of new surface epithelial cells, which are the hallmarks of endometrial repair, and is completed by cycle day 5. The finding of a significant regenerative response in endometrium during the menstrual period suggests previous endometrial degeneration. Indeed, syntheis of nuclear DNA was near zero levels in the secretory stratum functionale of the endometrium of body and fundus regions during cycle days 1 and 2. The findings are consistent with our previous ultrastructural observations, which have indicated that the stratum functionale, including the glandular, predecidual, and endothelial cells, undergoes irreversible cell injury from prior expulsion during periods of menstruation.[2] The observations are also in harmony with those of Epifanova,[5] according to whom secretory differentiation implies an arrest in cell growth on the one hand and a prelethal state on the other. However, Flowers and Wilborn,[6] after using electron microscopy with ruthenium red stain as an indicator for dead or injured cells, suggested that the secretory spongiosa remains viable during the menstrual period and is converted by autophagocytosis and heterophagocytosis of intra- and extracellular debris into a replicating endometrium. The discrepancies in observations may be attributed to different interpretations of cellular changes occurring during menstruation as well as different techniques used for sampling and studying uterine specimens.

In the present study, DNA syntheis was confined to the basal layer of the body-fundus of the uterus as well as the endometrial mucosa of the isthmus and peritubal ostia, all of which remained intact during menstruation. Significant increase in LI in these regions occurred only following complete denudation of the zona basale by cycle day 3. The sudden and marked rise in labeling intensity of the glandular epithelium, but not of stromal fibroblasts, in areas of denuded basal layer

and its sharp decrease coinciding with the appearance of resurfacing epithelial cells concur with the proposal that the newly formed surface lining derives principally from the persistent glandular epithelium of the basal layer.[1, 2, 7–10] A similar labeling pattern observed in the isthmic and peritubal ostia mucosae bordering the denuded endometrial cavity indicates their contribution to the peripheral repair of lost tissue. This contention is supported by experimental studies in the rabbit in which partial removal of the entire thickness of endometrial mucosa including the basal layer is reconstructed by the peripheral ingrowth of surface epithelial cells originating in the endometrium adjacent to mechanical denudation.[3, 11]

According to the present radiothymidine labeling study and previous ultrastructural observations,[1, 2, 10] postmenstrual endometrial repair involves both cellular migration and replication. The initial response was spreading and migration of new surface epithelial cells from the free stump of basal glands and peripheral wound edges into the denuded area. Migration was observed about six to 12 hours prior to increased DNA synthesis in the surface epithelial cells. This sequence of initial cellular expansion and subsequent cellular replication has also been observed in mechanically denuded rabbit endometrium.[3] Endometrial surface cells on the edge of denudation lacked DNA labeling and mitosis and were flattened with well-equipped, intracytoplasmic, microfilamentous-microtubular systems and pseudopodial projections.[1–3] These alterations have been ascribed to migrating-type cell populations in both in vivo and in vitro conditions.[3, 12, 13] The initial spread of first-produced, first-to-migrate surface lining appears to form an expanding network of cells over denuded area in which DNA synthesis and mitosis subsequently occur. This was evidenced by an increase of LI in surface cells as compared to the underlying basal cells during the third and fourth days of the cycle, which are dominated by wound healing reaction. As in the rabbit endometrial regeneration system, increased nuclear DNA activity and mitoses were correlated with maturation of surface cells from spindle shaped to cuboid and with repopulation of surface areas. DNA-mediated proliferative activity remained unchanged as the cuboid surface cells acquired a cylindrical shape and surface re-epithelialization was completed. Consequently, during the first six to 12 hours of the regenerative period starting from about day 3, spreading and migration appears to be the principal means to rapidly reconstitute endometrial integrity, whereas for the period thereafter, DNA synthesis, cell division, and migration continue simultaneously until a confluent surface layer has been regenerated, on cycle day 5.

Since significant increase of radiothymidine labeling of stromal fibroblasts and vascular endothelium was demonstrated in areas of active regeneration, it is reasonable to assume that these cells also participate in endometrial mucosal remodeling. Ultrastructurally, stromal fibroblasts were shown to be engaged in phagocytosis and presumably digestion of degenerated residual products of extracellular origin, whereas an increased number of organelles, principally free and bound ribosomes, enlarged cytoplasmic substance, and irregular membranes characterized endothelial cells of capillaries.[2, 3] Such endothelial alterations have been described in a variety of experimental injuries and are considered a reflection of regenerating type of endothelium.[12]

In an earlier communication, we have postulated that the new surface epithelium, characterized by negligible mitotic activity, nuclear enlargement, and abundant intracytoplasmic RNA synthesis, proliferates by endomitotic division,[2] On the basis of the present

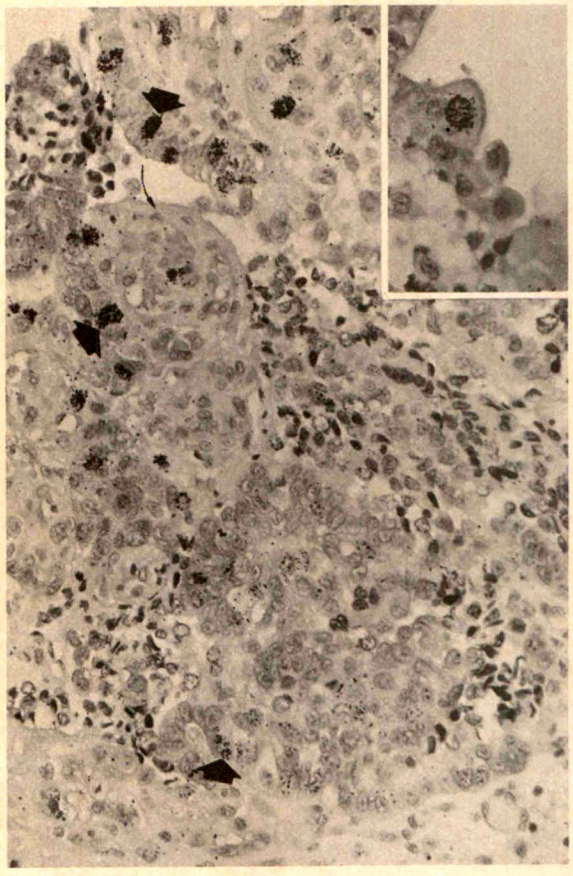


Fig. 6. Radioautograph of labeled surface epithelial cells (large arrows) displaying cuboid and columnar differentiation, on cycle days 3 and 4. Note lack of labeling in flattened variety of surface epithelium (curved arrow). (Hematoxylin and eosin. Magnification ×280.) Inset shows detail of nuclear labeling pattern of a cuboid surface cell. (Hematoxylin and eosin. Magnification ×400.)

study, the relative paucity of mitotic activity despite prompt restoration of postmenstrual endometrial surface may additionally be explained by (1) the distribution of replicating cell populations during periods of regeneration and (2) pattern of wound healing. Assuming that a complete cell cycle lasts about 10 hours, including eight hours for DNA synthesis and one hour for the mitotic phase, one would expect to see at least one cell in mitosis for every 10 cells labeled with radiothymidine. LI's of 6.0 and 1.7 per cent in basal glands in areas of denudation and surface regeneration, respectively, should therefore yield very few mitotic figures. The demonstration of an important migratory component devoid of mitosis during early periods of endometrial regeneration contributes further for the rarity of division figures.

The mechanism of induction of endometrial proliferation during menstruation is unknown. However, the lack of estrogen-related histologic and ultrastructural alterations in postmenstrual regenerating endometrium,[1, 2] together with DNA activity essentially limited to the regenerating epithelial and endothelial cellular systems and with low levels of plasma estradiol during cycle days 1 to 4, suggests that postmenstrual endometrial resurfacing is not influenced by estradiol-17β. This suggestion is supported by our previous observations on experimental endometrial regeneration in the rabbit, in which isotope uptake and ovariectomy-associated morphologic alterations of the regenerative but estrogen-deprived atrophic endometrium were similar to alterations in animals with intact ovaries.[3] On the other hand, the sudden increase in both nuclear DNA synthesis and mitosis in the stromal, vascular, and gland cell components of regenerated human endometrium on cycle days 5 to 7 and their further increase on cycle days 8 to 10[4] are consistent with preovulatory estradiol-17β–stimulated DNA synthesis and tissue growth.

In general, necrotizing injury causes cell death, thereby interrupting cellular integrity and continuity and resulting in proliferation. The observation of proliferation at the injury site as well as some distance from the wound area suggests the possibility of a diffusible substance(s) that would trigger migration and replication-mediated growth. Since endometrial repair is not initiated until complete denudation has occurred, it is also conceivable that repair of lost tissue is a function of temporary loss of inhibitor(s) of tissue growth, such as the tissue-specific, species-nonspecific inhibitor of mitosis, chalone.[14] Stabilization of DNA synthesis as the new surface epithelial cells reach maturation and complete re-epithelialization of the denuded zona basale may suggest proliferation-inhibition mechanism controlling wound healing.

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The baboon as a primate model for the study of endometrium

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A series of transcervical uterine biopsy specimens were obtained at various stages of the menstrual cycle from a colony of 11 normally cycling female baboons, *Papio anubis* and *Papio cynocephalus*. Morphologically, baboon endometrium appeared to be similar to human endometrium. Alkaline phosphatase activity was maximal throughout the preovulatory phase and during the late postovulatory period. During the preovulatory phase acid phosphatase was not demonstrable but increased after ovulation to reach maximal activity prior to menstruation. While differences exist between human and baboon endometria, the overall morphologic and histochemical changes are similar. In addition, the baboon's endometrium is readily accessible by transcervical uterine biopsy, thus making these animals valuable primate models for study of human reproductive problems.
(AM. J. OBSTET. GYNECOL. 134:305, 1979.)

MANY HISTOCHEMICAL and biochemical studies have shown that fluctuations occur in enzyme activity and carbohydrate content in the human endometrium throughout the menstrual cycle.[1] These endometrial alterations are under the control of the ovarian steroids, estrogen and progesterone, and are reflective of changes in plasma concentration of these two hormones.

In contrast to studies of human endometrium, only a few studies have been conducted on baboon endometrial modulations and none of these has focused on enzymatic distribution or activity throughout the menstrual cycle.[2-4] Because of the baboon's close phylogenic relationship to man, it is being used increasingly as a model in reproductive biology. In addition, the endometrium of the baboon can easily be sampled by transcervical biopsy. Therefore these animals could be valuable models in studies that require frequent sampling of the endometrium. However, prior to the acceptance of the baboon as a valid animal model, a more thorough evaluation of its menstrual cycle in terms of both physiologic and morphologic observations is needed. Thus, in the present study, acid and alkaline phosphatase activities were investigated in baboon endometrium and compared to the well-established fluctuations of those enzymes that occur in human endometrium.

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Material and methods

A colony of 11 normally cycling female baboons, *Papio anubis* and *Papio cynocephalus*, was used for this research. Daily records of sex skin turgescence and menses were kept for each of the animals. Both of these parameters enabled determination of the day of the menstrual cycle. An average menstrual cycle in our baboons was 32 days. The day of ovulation was determined[4] (day 0) and the cycle day identified as being before (−) or after (+) ovulation.

Endometrial tissue was obtained by transcervical uterine biopsy using a Novak curette after anesthetiz-

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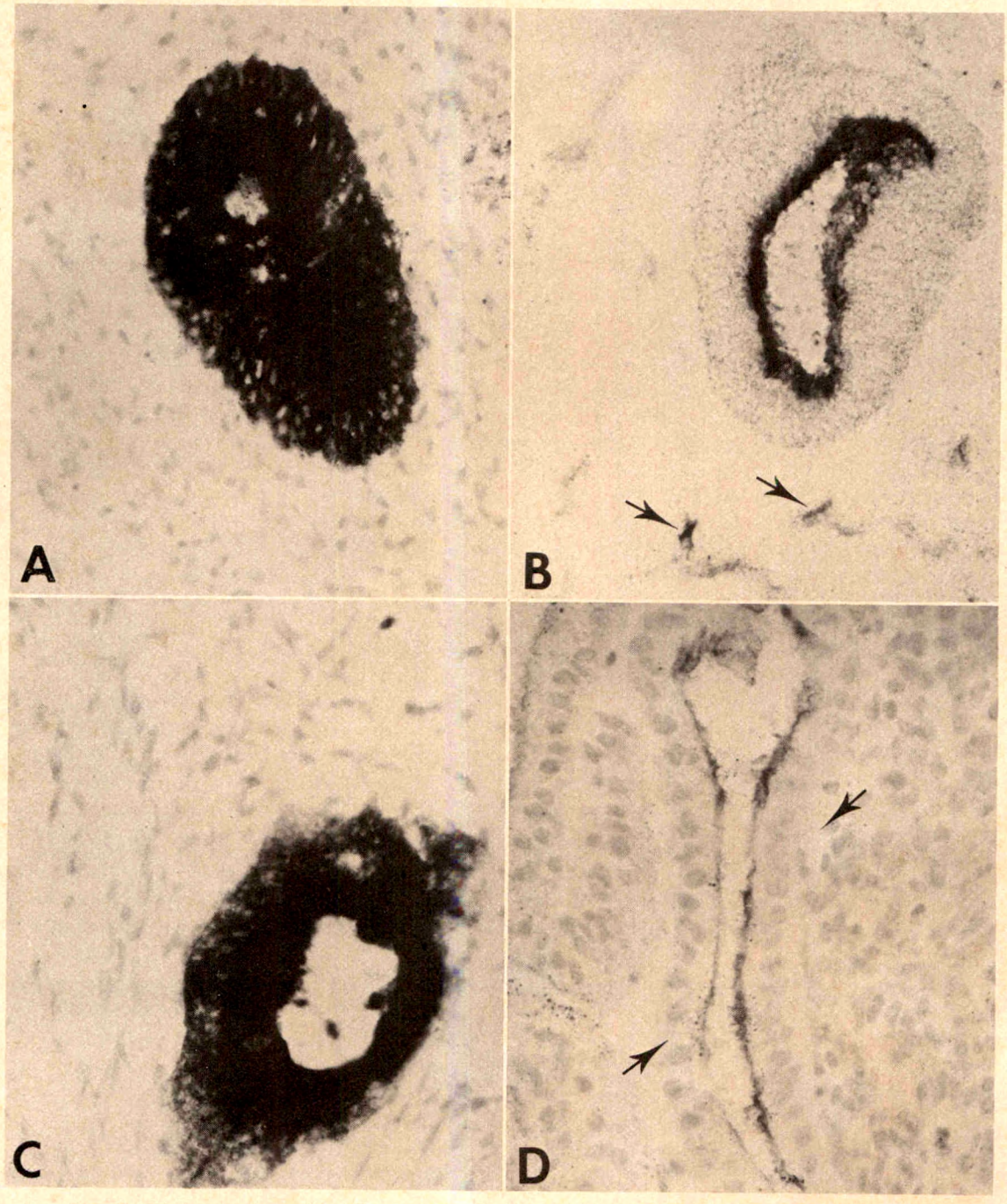


Fig. 1. *(A)* Alkaline phosphatase activity of endometrium during the preovulatory phase (day −2). The cytoplasm of the glandular cells is completely filled with reaction product. The stroma is unreactive for alkaline phosphatase. *(B)* Alkaline phosphatase activity of early postovulatory endometrium (day +3). Enzyme activity is distributed throughout the glandular cell cytoplasm, but they are most active in the apical cytoplasm. Enzyme activity is observed within the endothelium of blood vessels (arrows) scattered throughout the stroma. *(C)* Alkaline phosphatase activity of late postovulatory endometrium (day +15). A large gland filled with alkaline phosphatase reaction product is seen. No alkaline phosphatase activity is seen within the stroma. *(D)* Alkaline phosphatase activity of endometrium on the first day of menses. The endometrial glandular epithelium displays enzyme activity limited to the apices of the endometrial glandular epithelium (arrows). (Magnifications ×400.)

ing the animals with an intramuscular injection of ketamine HCl. Eighteen endometrial biopsy specimens (six preovulatory, 10 postovulatory, and two during menses) were obtained for light microscopic and histochemical evaluation.

One half of the endometrial sample was fixed in neutral buffered formalin (10 per cent for 24 hours at 4° C., embedded in paraffin, sectioned at 6 μm, and stained with hematoxylin and eosin. The other half of the endometrial sample was rapidly frozen on dry ice and sectioned at 10 μm in a cryostat at −20° C. These sections were incubated for the demonstration of either acid or alkaline phosphatase by two different techniques. One was a modification of the original Gomori metal salt procedure[5] while the other involved an azo dye technique.[6] In all controls for the alkaline phosphatase reaction the substrate was omitted. For acid phosphatase, the control consisted of the addition of 0.01M sodium fluoride to the media. All sections were incubated in Coplin jars for 30 minutes at 37° C.

Results

Histology. The histologic changes that occurred in baboon endometrium during the menstrual cycle correlated with the changes that have been described in human endometrium,[7] thus confirming previous reports by MacLennan and Wynn[2] and Kraemer and colleagues.[4] In addition, granulated endometrial stromal cells were observed infrequently in the last half of the postovulatory period in the baboon. These cells contained small eosinophilic granules within their cytoplasm and resembled the granulated endometrial stromal cell that has been described in human endometrium[8] and macaque endometrium.[9]

Histochemistry. The results obtained with either the modified Gomori metal salt method or the azo dye technique correlated for all phases of the menstrual cycle. Controls for acid and alkaline phosphatase activity were negative.

Alkaline phosphatase. Maximal alkaline phosphatase activity, limited to the endometrial glands, is demonstrable throughout the preovulatory phase (days −14 to −1). The activity of the enzyme within the glands, exhibited as a dark precipitate, is evenly distributed throughout the cytoplasm (Fig. 1, *A*).

During the early postovulatory phase (days +1 to +7), overall alkaline phosphatase activity decreases. However, activity within the supranuclear cytoplasm remains high (Fig. 1, *B*), while the perinuclear and subnuclear areas demonstrate a marked decrease in activity. The stromal cells fail to exhibit alkaline phosphatase activity.

During the last half of the postovulatory phase (days +8 to +16), alkaline phosphatase achieves maximal levels comparable to those of the preovulatory period (Fig. 1, *C*). Heavy precipitation is observed in all areas of the glandular cells and the lumen is partially occluded. However, stromal cell activity is still negligible.

Alkaline phosphatase activity on the first day of menses shows a drastic decline, generally being the lowest seen during the menstrual cycle. Enzyme activity is present only as trace amounts within the apices of the endometrial glandular cells (Fig. 1, *D*). The stromal cells show no alkaline phosphatase activity.

Acid phosphatase. Acid phosphatase activity was not demonstrable throughout the preovulatory phase (days −14 to −1) (Fig. 2, *A*). This observation was true for both the stroma and the endometrial glands.

During the early postovulatory phase (days +1 to +7) acid phosphatase activity began to increase within the endometrial glandular cells. This activity, displayed as a dark precipitate, is most noticeable within the apices of the glandular cells (Fig. 2, *B*). However, trace amounts of granular reaction product are distributed diffusely throughout the cytoplasm of the glandular cells. Certain glandular cells show clumps of precipitate located within the basal region of the cells. The stroma, except for a few scattered granules, is negative for acid phosphatase reaction.

In the late postovulatory phase (days +8 to +16), acid phosphatase activity increases to its highest level within the glands (Fig. 2, *C*). Both the lumen and supranuclear cytoplasm are completely filled with reaction product. Within the subnuclear cytoplasm, the enzyme's activity is not as great, while activity in the stromal cells remains unchanged from that of the early postovulatory phase.

Striking changes are observed on the first day of menses. Acid phosphatase activity is diminished and is primarily concentrated in either the subnuclear or supranuclear cytoplasm (Fig. 2, *D*). The stroma, which until now has been essentially negative for acid phosphatase, contains numerous, evenly dispersed, fine granules.

Comment

In the present study, the acid phosphatase activity of baboon endometrium parallels the activity observed in women.[10] Acid phosphatase could not be demonstrated during the preovulatory phase and first appeared during the early postovulatory period. Enzyme activity continued to increase during the postovulatory phase and reached a peak prior to menstruation. During menstruation, acid phosphatase activity could be dem-

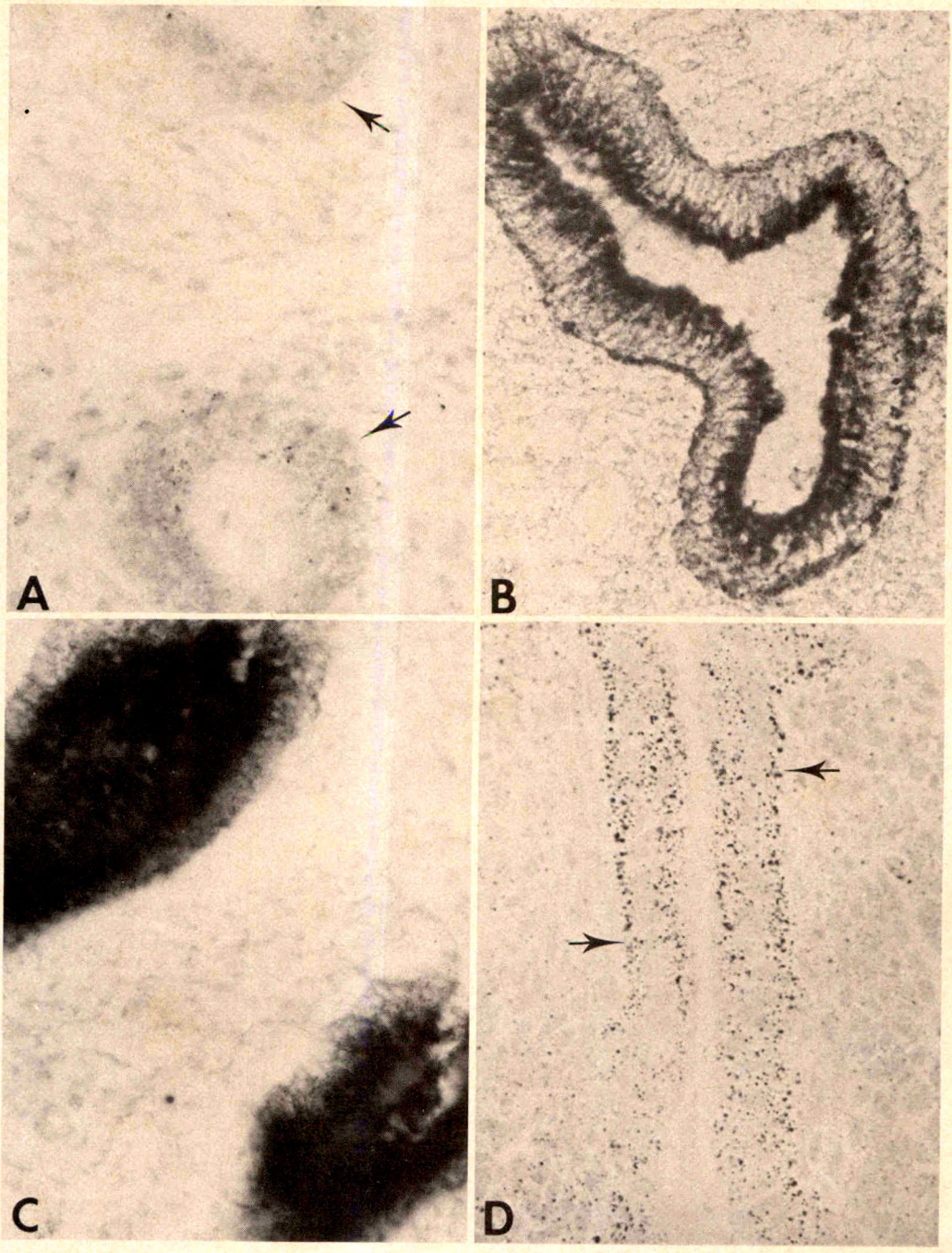


Fig. 2. *(A)* Preovulatory endometrium (day −3) reacted for acid phosphatase. The stroma and portions of two endometrial glands (arrows) are shown. No activity is observed in either element. *(B)* Acid phosphatase activity of early postovulatory endometrium (day +3). The heaviest activity is located within the apices of the glandular cells; however, some precipitate is dispersed throughout the cytoplasm. *(C)* Acid phosphatase activity of late postovulatory endometrium (day +15). Acid phosphatase activity in the glandular cells increases during the late secretory period. Extensive activity is observed within the supranuclear cytoplasm. *(D)* Acid phosphatase activity of endometrium on the first day of menses. Within the glandular epithelium (arrows), acid phosphatase activity is evenly distributed between the apical and basal regions of the glandular cells. Acid phosphatase activity is also demonstrable for the first time within the stromal cells. (Original magnifications ×400.)

onstrated within the baboon stromal cells, as it was in human studies.[11]

Alkaline phosphatase in the baboon displayed maximum activity throughout the preovulatory phase and again in the late postovulatory phase. In contrast, the enzyme's activity decreased immediately after ovulation. In women, alkaline phosphatase reaches a peak prior to ovulation and then begins to decline during the postovulatory phase.[12] These enzyme fluctuations in women are thought to be under hormonal control; presumably estrogen stimulates alkaline phosphatase activity while progesterone is an inhibitor. In the present study, the decrease in alkaline phosphatase activity after ovulation correlated with a decline in plasma estrogen levels and increasing progesterone levels.[13, 14] The increased alkaline phosphatase activity observed during the late postovulatory phase occurs at a time when the estrogen levels are similar to those detected in the preovulatory phase and when progesterone is again approaching preovulatory levels. Thus it appears that baboon endometrial alkaline phosphatase is under control of ovarian hormones in a manner identical to that in women.

In summary this study supports the conclusions by MacLennan and Wynn[2] that the morphologic features of baboon endometrium are similar to those of human endometrium. In addition, our histochemical observations are similar to other findings in human endometrium. Such findings suggest that the baboon would be a satisfactory primate model for the study of human reproductive problems. In addition, the accessibility of the baboon's endometrium makes these animals particularly useful in studies that require frequent sampling of endometrium. Because of the similarity of the baboon and human menstrual cycles and the accessibility of the baboon's endometrium, it could be extremely valuable in studies that may present too great a risk if conducted in women.

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A syndrome characterized by recurrent symptomatic functional ovarian cysts in young women

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A syndrome characterized by the persistent recurrence of symptomatic functional ovarian cysts, elevated plasma estradiol levels, and infertility in four young patients is described. Two of the patients experienced recurring ovarian cysts following total abdominal hysterectomy and bilateral salpingo-oophorectomy. Pathologic findings confirmed the presence of ovarian tissue in all cysts. Recurrent cysts formation is attributed to either an increased production of gonadotropins or a hypersensitive response to normal gonadotropins. The development of recurrent cysts following bilateral oophorectomy indicates that some ovarian or "ovarian-like" tissue is present within the pelvic cavity, anatomically unrelated to the normally positioned ovaries. This extraovarian tissue may become sensitive to circulating gonadotropin levels in the absence of normal ovarian tissue. The source of this extraovarian tissue is discussed from an embryologic standpoint. (AM. J. OBSTET. GYNECOL. 134:310, 1979.)

BENIGN OVARIAN CYSTS are commonly classified as either nonneoplastic or epithelial.[1] Nonneoplastic cysts can be functional, that is, they respond to circulating estrogens and gonadotropins.[1, 2] Functional ovarian cysts of this type may develop as a result of a hypothalamic-pituitary dysfunction with an abnormal process of cyclical follicular maturation and corpus luteum formation.[1]

Follicle cysts, the most common type of functional cyst, are usually small and asymptomatic. They generally undergo spontaneous resorption and, thus, for the most part remain undiagnosed. On occasion, however, such cysts become large enough to produce discomfort or pain. They may become hemorrhagic and torsion of the pedicle may occur.[1] Such functional cysts are capable of producing estrogen[3] and are the most common cause of pseudoprecocious puberty in girls.[1, 4] The appearance of functional follicular cysts during the normal reproductive life of women may cause irregular menstrual cycles.[1, 2]

Treatment of young women is expectant and ovarian suppression is advocated to accelerate the process of resorption.[1, 2] Surgical intervention is rarely indicated since such cysts disappear spontaneously.[2]

The present report details the persistent recurrence of symptomatic functional cysts and accompanying elevations of plasma estradiol levels in four young patients. Two of the patients experienced recurring cysts following total abdominal hysterectomy and bilateral salpingo-oophorectomy. The others developed recurrent ovarian cysts upon interruption of ovarian suppression. These symptoms were accompanied by infertility. This study offers explanations of this syndrome and suggests that such condition may not be as rare as generally indicated.

Case reports

Case 1. V. B., a 28-year-old, white woman, gravida 0, had a long history of primary infertility, irregular cycles, and anovulation. Prior to consultation in our Section of Reproduction, this patient experienced recurrent symptomatic ovarian cysts necessitating exploratory laparotomy on two occasions. On each occasion large, simple follicular cysts were removed. During the last surgical procedure, bilateral ovarian wedge resection and cauterization of pelvic endometriosis were also performed. She was placed on a regimen of oral contraceptive therapy for several months.

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Pain and a right lower quadrant mass recurred a few weeks after discontinuation of the ovarian suppression, at which time she was referred to us. A right pelvic mass adjacent to the uterus was easily palpable and the plasma estradiol level was 102 pg/ml. Suppression of the mass with oral contraceptives (Norlestrin, 2.5 mg) was initiated. Within three weeks the right adnexal mass had disappeared and the plasma estradiol level had decreased to 11 pg/ml. Oral contraceptive suppression was stopped.

Three weeks later the patient returned, again complaining of right lower quadrant pain. A right pelvic mass was palpable and the plasma estradiol level had risen to 149 pg/ml. A regimen of long-term ovarian suppression was started and has continued for the past six months. This patient strongly desires to become pregnant.

Case 2. S. Z., a 21-year-old, white woman, gravida 0, had a long history of recurrent ovarian cysts beginning at age 10. Exploratory laparotomy at that time revealed a 10 cm left ovary, twisted and infarcted. The right ovary was also enlarged and cystic. A left oophorectomy and partial resection of the right ovary were performed. Pathologic findings revealed both ovaries to contain serous, hemorrhagic follicular cysts with stromal hemorrhage and capsular fibrosis.

The patient began using oral contraceptives at 14½ years of age. Later, the patient desired pregnancy and oral contraceptives were discontinued. One month later, she complained of right lower quadrant abdominal pain. Pelvic examination revealed a 6 to 8 cm right adnexal mass.

Oral contraceptive therapy was reinitiated and two weeks later she was asymptomatic and the cystic mass had decreased in size. Oral contraceptives were administered for only one cycle. One month later the patient again complained of right lower quadrant abdominal pain associated with nausea and dizziness. Plasma estradiol at this time was 581 pg/ml. Oral contraceptives were again begun and the patient displayed subjective improvement after 5 days of hormonal suppression, at which time pelvic examination revealed a smaller right ovary and a plasma estradiol level of 21 pg/ml. The patient remained asymptomatic for one year with normal pelvic examinations. Ovarian suppression was then stopped.

One month later she complained of abdominal pain and a pelvic examination revealed the right ovary to be 5 cm in diameter. She was observed without therapy for 2 weeks, remaining symptomatic. Oral contraceptives were begun again and the pelvic examination became normal. The patient, presently on a regimen of long-term oral contraceptive therapy, remains asymptomatic with low plasma estrogen levels. However, she still desires pregnancy.

Case 3. P. M. M., a 26-year-old, white woman, gravida 1, para 1, had a normal delivery in 1971. Following delivery the patient used oral contraceptive therapy intermittently for one year. One month after cessation of oral contraceptives the patient developed heavy vaginal bleeding and a large right ovarian cyst. This was to mark the beginning of several years of almost constant symptomatology as a result of frequent recurrent cysts.

She underwent laparoscopy followed by laparotomy and removal of the right ovarian cyst. A bilateral wedge resection was also performed with the clinical impression of polycystic ovarian syndrome that was not confirmed by pathologic examination.

One month following operation, a cystic, tender adnexal mass was palpated. For the next year and a half, she had numerous episodes of low abdominal pain, irregular vaginal bleeding, and palpable pelvic masses, treated intermittently with oral contraceptives and estrogen therapy. She was finally hospitalized for pulmonary embolism, at which time estrogen therapy was stopped.

Six months after estrogen treatment was stopped, she developed severe left lower quadrant pain and a large, left, tender, cystic mass was palpated. Exploratory laparotomy was performed during which a left salpingo-oophorectomy was done, in addition to freeing of multiple pelvic adhesions. One month later she developed severe low pelvic pain and a right cystic adnexal mass (6 cm) was easily palpable. Due to this chronic problem she underwent a total abdominal hysterectomy and right salpingo-oophorectomy. One month later she developed left lower quadrant pain and a left lower pelvic mass was again palpated and treated with ovarian suppression. A year later she developed right lower quadrant pain and a pelvic mass was palpated and confirmed on ultrasound. Operation was performed during which a large pelvic mass was removed from the vaginal cuff with dissection of multiple pelvic adhesions. The presence of ovarian tissue was confirmed by pathologic examinations. Nine months later she underwent another exploratory laparotomy for symptoms of bowel obstruction. No mass was found and lysis of multiple intestinal adhesions was performed.

Three months later she returned, complaining of severe progressive dyspareunia. Large, bilateral, tender pelvic masses were easily palpable. Exploratory laparotomy revealed two large cystic masses that were removed. Pathologic diagnosis confirmed the presence of active ovarian tissue.

She was referred to us two weeks after operation. She had no complaints and a pelvic examination proved negative. The plasma estradiol level was 7 pg/ml. She was placed on a regimen of medroxyprogesterone acetate (Depo-Provera, 150 mg intramuscularly). Long-term suppression was planned with the need for further medroxyprogesterone acetate injections to be periodically evaluated by determinations of plasma estradiol levels. She again developed severe lower abdominal pain and dyspareunia and a right cys-

tic mass was felt attached to the vaginal cuff. The plasma estradiol level was less than 5 pg/ml but three days later she underwent a seventh laparotomy. A large cystic mass was removed from the right pelvis and multiple intestinal adhesions and numerous nodules were found throughout the abdominal and pelvic cavities. The pathologic diagnosis was "peritoneal cyst, foreign body reaction, chronic inflammation, fatty degeneration, and fibrosis." No ovarian tissue was identified. She has been kept on a regimen of medroxyprogesterone acetate, and the plasma estradiol levels have remained less than 5 pg/ml for the past four months.

Case 4. D. L., a 24-year-old, white woman, gravida 0, had a long history of recurrent ovarian cysts. A uterine suspension and left cystectomy were performed for a left pelvic mass, after which the patient was placed on a regimen of oral contraceptives (Ortho-Novum 1 + 50) for two years. Three months after stopping oral contraceptive therapy, she complained of abdominal pain. Laparoscopy revealed an 8 by 8 cm right follicular cyst from which 75 ml of blood was aspirated. Because of dense adhesions to the pelvic colon, no left adnexa could be clearly identified.

Two months later pain and a left adnexal mass developed. At laparotomy a large left ovarian cyst was found with dense adhesions to the colon and uterine wall. The cyst was multilocular with very thin walls and leaked a clear hemorrhagic fluid when incised. The left cyst was dissected from the ovary and an "endometrioma" removed from the right ovary. Pathologic findings revealed corpus hemorrhagica in the right sample and normal ovarian tissue with corpus albicans and hemosiderin deposit in the left. No endometriosis was found.

Five months later the symptomatology reappeared in the left lower quadrant. A blood sample was taken and sent to our laboratory. An elevated plasma estradiol level of 557 pg/ml was reported. Ovarian suppression with oral contraceptives was started. The patient became asymptomatic with plasma estradiol levels decreasing to 79 pg/ml in one month and to 24 pg/ml the second month.

Six months later ovarian suppression was terminated because of side effects. Following cessation of treatment, the patient again developed left lower quadrant pain and a palpable left ovarian cyst. An exploratory laparotomy (the fourth surgical procedure) revealed multiple pelvic adhesions, several left ovarian cysts (one measuring 5 by 7 cm), and complete obliteration of the architectural structure of the pelvic cavity. A complete loss of the adnexal anatomy on both sides without evidence of tubal patency prompted a total abdominal hysterectomy and bilateral salpingo-oophorectomy.

Eight months following operation the patient consulted our Section of Reproduction, complaining of similar symptomatology ongoing for the past few months. Plasma estradiol level was 272 pg/ml and a large left adnexal mass was palpated at that initial visit. A month later the plasma estradiol level was 234 pg/ml. Ovarian suppression was begun and the plasma estradiol level dropped to 7 pg/ml in 2 months. All symptoms disappeared and estradiol levels were maintained around 20 pg/ml.

Ovarian suppression was again interrupted because of side effects. Within a short time the left lower quadrant pain reappeared and the plasma estradiol level increased to 281 pg/ml. A soft, irregular mass could be felt in the left adnexal area. The patient refused further suppression and demanded a "final surgical solution." Exploratory laparotomy revealed a large, thin-walled, multiloculated cyst attached to the pelvic colon. The cyst along with periureteral tissue and a portion of the serosal peritoneum of the colon was removed in an effort to eliminate any remaining ovarian tissue. Five days after operation the estradiol level had dropped to 6 pg/ml. She was again placed on a regimen of ovarian suppression therapy.

Four months later the patient decreased the estrogen dosage in half because of weight gain. Three weeks later she developed progressive colic pain in the left costovertebral angle. She was admitted to the hospital with the diagnosis of kidney stone. An intravenous pyelogram showed possible external compression of the left ureter and mild left hydronephrosis. A large, very painful cystic mass fixed to the pelvic wall was palpated. A retrograde catheter was placed in the left ureter and her symptoms improved. The plasma estradiol level was 86 pg/ml and suppression with medroxyprogesterone acetate (Depo-Provera, 150 mg intramuscularly) and an oral contraceptive (Norlestrin, 2.5 mg twice daily) was started. A second intravenous pyelogram 7 days later revealed no further extrinsic compression of the ureter and a smaller and less painful mass was felt on pelvic examination. The patient was discharged on a regimen of oral contraceptives (Norlestrin, 2.5 mg/day) with a plasma estradiol level of 16 pg/ml and with plans for prolonged suppression with medroxyprogesterone acetate. She has remained asymptomatic for the past 4 months and monthly estradiol levels are between 14 and 18 pg/ml.

Comment

Patients with ovarian cysts are frequently found in clinical practice.[1] However, reports of ovarian cysts of the functional type are uncommon since the vast majority of these are asymptomatic and pass undiagnosed. Most regress spontaneously or after ovarian suppression never again to affect the patient.

The four patients described in this report present a similar, interesting, and unusual clinical syndrome characterized by the frequent recurrence of functional ovarian cysts. The cysts were symptomatic to the point of necessitating repeated surgical intervention and prolonged ovarian suppression with oral contraceptives. Each episode, characterized by pain and adnexal mass,

was accompanied by elevated plasma estradiol levels in three of the four patients in whom blood studies are available. The pathology report confirmed the presence of ovarian tissue in each case. During ovarian suppression, these patients remained asymptomatic, plasma estradiol levels were low, and the patients were free of pelvic masses.

Reports of recurrent ovarian cysts, such as those present in our group of patients, are most uncommon. Several explanations may be offered to elucidate the etiology of this syndrome. One causative factor may be an increased production of gonadotropins. It would appear that these ovarian cysts did not develop in response to elevated gonadotropins, as occurs in molar pregnancies, or from a complication of ovulation induction,[1, 2] since elevated gonadotropins were not found on any occasion. Whether a considerable rise in gonadotropin levels occurred before the appearance of the cysts is not known, since no hormonal levels were obtained prior to the patients' becoming symptomatic and since normal low levels of gonadotropins found during the cyst-free periods were the direct result of the ovarian suppression therapy. It is possible, therefore, that high gonadotropin levels may have initiated growth of the cysts and then decreased as a result of the elevated estrogen production by the cyst, at which time the patient sought consultation.

A second explanation may be that the ovarian tissue elicits a hypersensitive response to normal gonadotropins by forming these recurrent functional cysts. Such hypersensitivity of ovarian tissue could be due to an unknown error in the metabolic pathway of granulosa and/or theca cells. This hyperresponse to normal gonadotropin levels could be the counterpart of the unresponsive ovarian syndrome in which normal ovarian tissue does not respond to normal or increased gonadotropin levels.[5, 6] The mechanism by which normal-appearing follicles fail to respond to gonadotropins is not clear.

The above possibilities can be used to explain the clinical manifestations in Cases 1 and 2. However, they cannot provide the complete explanation of the recurrence of "ovarian-like" cysts following bilateral oophorectomy in Cases 3 and 4. The ovarian cellular composition of the recurring cysts along with the increased estrogen levels indicates that there is some ovarian or "ovarian-like" tissue within the pelvic cavity that responds to normal gonadotropin levels.

Ovarian tissue remaining within the pelvic cavity following bilateral oophorectomy could be a result of one of the following:

1. Incomplete surgical removal of the ovaries is a possibility since the oophorectomy was performed after several surgical procedures which have produced extensive pelvic adhesions and distortion of the normal position of the ovaries. However, this possibility seems remote since extreme caution was exercised at the time of oophorectomy and in the surgical procedures performed after bilateral oophorectomy to ensure complete removal of all ovarian tissue.

2. Accessory ovaries in which the extraovarian tissue is situated near to and usually connected with the normally placed ovary could be the source of the recurrent follicle cysts. Origin of such accessory ovaries is probably similar to that of the normally placed ovaries. Usually this accessory ovarian tissue is quite small and thus remains unrecognizable prior to pathologic evaluation. Wharton[7] in an excellent review article reported only 18 authors who had described this pathologic finding with only three seeing more than one case. In all of these cases tissue with the distinct structure and function of a normal ovary was present. Our two cases do not appear to be conditions of accessory ovaries since the cystlike structures were distant from and not connected to the site of the normal ovaries.

3. Another possibility involves the formation of extraovarian tissue not associated with the normally placed ovary. Wharton[7] described a rare condition called supernumerary ovary in which ovarian tissue was located in a position not associated with that of normally placed ovaries. These supernumerary ovaries may be functional. Kosasa and associates[8] reported on one patient with elevated total plasma estrogen after bilateral oophorectomy. The source of the estrogen was a retroperitoneally located supernumerary ovary. Wharton[7] theorized that such aberrant ovaries were the result of the failure of migrating germ cells to reach the developing genital ridge. That such germ cells do find their way to extragonadal areas and are viable and may be the source of tumors has been demonstrated in a variety of animal species.[9] Such primary germ cell tumors have been found in the anterior mediastinum[10] and in a retroperitoneal location.[11]

In our study, the pathologic findings show the cysts to contain granulosa luteal and theca luteal cells and ovarian stroma. No oocytes were observed. In association with Wharton's theory, presumably the extragonadal germ cells induced the surrounding mesenchymal cells to differentiate into ovarian cellular components. Another explanation would be that of Printz and associates[12] who reported a case of a 23-year-old, black woman in which they found ovarian tissue embedded in the omentum. They theorized that a portion of the genital ridge, after colonization by the germ cells, became detached and then reattached in a neighboring area. This would explain the normal ovarian

tissue contents of the cyst in the pathologic findings.

From our findings it appears that whatever the source of this ovarian tissue it becomes functional and produces large amounts of estradiol to levels much higher than those found after the removal of both normal ovaries. Such tissue may become extremely sensitive to circulating gonadotropins in the absence of normal ovarian tissue. Greenwald[13] showed in hamsters that after unilateral ovariectomy the remaining ovary hyperovulates. Biskind and Biskind[14] in rats and McLaren[15] in mice demonstrated that an ovary transplanted to the spleen hypertrophied only after the in situ ovary was also removed. Furthermore, Chihal and associates[16] demonstrated that "extraovarian" tissue affects the number of eggs ovulated and the plasma levels of progesterone in postpuberal rats receiving ovarian homografts. This has not been shown in humans; however, it is certainly possible that aberrant embryonic gonadal tissue in the absence of normal ovarian tissue may develop under the influence of normal gonadotropins and thus be responsible for recurrent ovarian cyst formation.

Infertility is an important secondary effect of either the syndrome or its long-term therapy. Only one of the patients presented here has been pregnant and this occurred prior to the development of the syndrome. Despite the desire for children in Patients 1 and 2, ovarian cysts have developed each time ovarian suppression was stopped.

The development of recurrent ovarian cysts either before or after bilateral oophorectomy is considered rare. It is possible that this syndrome may be more prevalent than a review of the literature leads one to believe. In fact, we have diagnosed four cases of this condition in the past two years.

The need for ovarian suppression and the monitoring of long-term therapy with plasma estradiol levels is recommended. Surgical approach to treat this syndrome does not seem adequate, and after the first recurrence probably no further surgery is indicated. Presently we find no alternative to ovarian suppression for the treatment of these patients. It is possible that this syndrome may regress after menopause, a time at which the ovary does not normally respond to markedly elevated gonadotropin levels.

We hope that by characterizing this syndrome we will encourage more reports of patients like these and therefore find a better way of evaluating and treating recurrent symptomatic functional ovarian cysts.

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Optimum dosage of an oral contraceptive

A report from the study of seven combinations of norgestimate and ethinyl estradiol

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A statistically designed study was carried out to determine an optimum combination of norgestimate and ethinyl estradiol as an oral contraceptive, based on efficacy, safety, and side-effect patterns. A total of 1,991 patients were studied for more than two years while they were receiving various dosage combinations of these steroids. There were seven dosage combinations studied as part of a statistically orthogonal experimental design, augmented by three combinations near the center. The data arising from these studies were used to fit approximate functions relating the amount of norgestimate and ethinyl estradiol to the rate of spotting and breakthrough bleeding, gastrointestinal disturbance, and pregnancies. These functions, in turn, helped to identify an optimum dosage (0.125 mg. of norgestimate plus 0.035 mg. of ethinyl estradiol) in the entire range of combinations studied. (AM. J. OBSTET. GYNECOL. 134:315, 1979.)

THE MOST WIDELY USED oral contraceptives are combination products that consist of a synthetic estrogen and progestin. These drugs are extremely effective and possess a relatively high degree of safety. However, through the years there have been continued efforts to seek effective lower-dose forms of these drugs. In the late 1960's, researchers Inman and Vessey[1] in Great Britain, Sartwell and associates[2] in the United States, and others reported an association between the use of oral contraceptives and an increase in the risk of certain types of thromboembolic diseases. Later, Inman and associates[3] reported a positive correlation between the risk of these diseases and the dose of estrogen in an oral contraceptive. It has also been reported that certain side effects commonly attributed to the use of oral contraceptives (i.e., nausea, headache, nervousness) are related to the amount of estrogen in the contraceptive. In April, 1970, both the United States Food and Drug Administration[4] and the Medical Committee of the International Planned Parenthood Association[5] issued statements recommending the use of oral contraceptives containing the lowest effective levels of estrogen whenever possible.

Since 1970, there have been reports in the literature demonstrating the efficacy and side-effect patterns of oral contraceptives with dosages lower than those of previously marketed products. Bye and Elstein[6] and others[7, 8] have shown that combination contraceptives containing less than 0.05 mg. of ethinyl estradiol (EE) are effective in preventing pregnancies. One disadvantage to reducing the dosage of estrogen in oral contraceptives is the fact, reported independently in several articles,[7–9] that annoying intermenstrual bleeding, such as spotting or breakthrough bleeding (BTB), increases. Spotting and BTB rates are influenced not only by the amount of estrogen in an oral contraceptive but also by the ratio of the amounts of estrogen and progestin.[10] This makes the selection of an appropriate dosage for a low-dose oral contraceptive difficult.

There have been reports in the literature[7, 9] of clini-

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Table I. Dosage regimens of norgestimate and EE

Regimen	*Progestin (norgestimate) (mg.)*	*Estrogen (EE) (mg.)*
A	0.250	0.020
B	0.250	0.050
C, P, R	0.125	0.035
G	0.060	0.020
H	0.060	0.050
O	0.090	0.030
T	0.125	0.025

Table II. Number of patients completing each cycle

	Regimen						
Cycle	*A*	*B*	*C, P, R*	*H*	*G*	*O*	*T*
1	100	117	1398	97	97	195	197
2	98	116	1304	95	94	191	182
3	94	114	977	90	90	188	174
4	89	113	552	86	83	183	113
5	80	109	529	81	78	181	90
6	79	105	515	80	73	177	34
7	76	102	505	77	71	174	–
8	75	100	478	75	65	168	–
9	73	93	460	71	56	162	–
10	68	90	294	67	29	–	–
11	63	81	155	60	2	–	–
12	37	49	132	32	1	–	–
13	2	20	77	–	–	–	–
14	–	–	74	–	–	–	–
15	–	–	70	–	–	–	–
16	–	–	69	–	–	–	–
17	–	–	66	–	–	–	–
18	–	–	64	–	–	–	–
19	–	–	64	–	–	–	–
20	–	–	63	–	–	–	–
21	–	–	48	–	–	–	–
22	–	–	23	–	–	–	–
23	–	–	2	–	–	–	–

cal studies comparing several regimens of lower-dose combination oral contraceptives for purposes of selecting an optimum combination and/or determining the relationship of bleeding patterns/efficacy to the dosage of the product. Because bleeding patterns are affected not only by the dosage of estrogen and progestin but also by the ratio of the two components, and since an optimum combination of two steroids may not be one of the regimens selected for a study, extremely sensitive study designs (i.e., selection of study regimens) and efficient methods of data analysis are needed for these types of studies. Application of statistica response surface methods[11] seems appropriate in this situation.

Response surface methods are a collection of mathematical and statistical procedures useful in studies where a response (numerical measure of the outcome of an experiment) is influenced by other independent variables that can be controlled. The procedures consist of experimental designs (i.e., methods for selecting several combinations of levels of independent variables for experiments), regression techniques (i.e., methods of fitting an approximate functional relationship between the response measurement and the independent variables), and mathematical procedures for exploring the fitted function or surface (i.e., predicting the response at levels of independent variables where no experiments have been conducted, finding the combination of minimum response, etc.).

For the problem of studying the effect of dosage in low-dose oral contraceptives, the independent variables are, of course, the dosage of estrogen and progestin, and the response may be pregnancy rate or severity of side effects (i.e., bleeding irregularities, gastrointestinal disturbance, etc.).

Material and methods

The purpose of this study was to determine the relationship between the dose of estrogen (EE) and progestin (norgestimate) in an oral contraceptive to the efficacy and side-effect patterns. Also, it was of interest to find the optimal combination of norgestimate and EE for the purpose of oral contraception. To accomplish this purpose, seven dosage regimens of norgestimate and EE were studied clinically. These regimens are listed in Table I.

The study was conducted in Mexico City, Mexico, between March, 1973, and December, 1974, and represents the effort of nine investigators. There were four separate protocols. The first protocol was an open study in which regimens A, B, C, G, and H were compared (Table I). The second protocol was a double-blind study in which regimen O was compared with regimen P (same dosage as C, Table I).

The third protocol was double blind and regimen T was compared with regimen R (same dosage as regimens C and P, Table I). The fourth protocol was an open study of regimen R.

Selection of patients for all protocols was determined by the following criteria: good general health, proved past fertility, absence of pregnancy, reproductive age (17 to 40 years), regular menstrual periods, and regular coitus. Patients who exhibited disorders commonly accepted as contraindicating sex hormone therapy, such as thrombophlebitis or thromboembolic disorders, pulmonary embolisms or cerebral apoplexy, cardiovascular disease, marked impairment of liver function, undiagnosed abnormal vaginal bleeding, known or suspected carcinoma of the breast or genital tract, history of any chronic disease, significant past or present illness, neurovascular lesions of the eye or visual disturbance, or a Class III or greater Papanicolaou smear, were excluded from the study.

Prior to admission, each patient had a complete history and physical examination, with special emphasis on breast and pelvic examinations. These examinations were repeated at approximately yearly intervals thereafter. In addition, routine laboratory and ophthalmologic examinations were performed on a subset of patients.

Upon entry into the study each patient was randomly assigned to one of the seven dosage regimens. The drug was administered orally as a 21 day cyclic regimen, three weeks with medication followed by one week without. Tablets were packaged in the manufacturer's Dialpak* tablet dispenser and patients returned after each cycle to obtain additional tablets. At each visit patients were interviewed and the blood pressure and weight were recorded. Any vaginal bleeding occurring on days of pill ingestion, which was not the result of the last menstrual period, was classified as spotting or BTB.

Some patients who were originally assigned randomly to one of the seven dosage regimens were later reassigned as new patients to the R regimen (0.125 mg. of norgestimate + 0.035 mg. of EE), since study on that regimen was continued after the other regimens were discontinued. Comparisons revealed no differences in the age distribution of patients studied in each regimen or the range and average of age at menarch, past pregnancies, and number of deliveries and abortions for patients in each regimen.

The data of interest, with respect to analysis, were counts of the number of cycles in which spotting or BTB occurred, percentage of patients with gastrointestinal disturbance during the first cycle of use, and number of pregnancies. Life-table[12] estimates of pregnancy rates were made and cycle percentages of spotting and BTB occurring in the stabilized region were calculated. With the minimum χ^2 estimation approach,[12–14] three response surfaces, or functions, were found, relating the cycle per cent of spotting and BTB, per cent of gastrointestinal disturbance, and the pregnancy rate to the estrogen and progestin dose. Empiric sampling studies have shown this approach to be good even in cases where failure rates are very low, as in the case of pregnancy rates in oral contraceptive studies.

Results

Table II shows the number of patients completing each cycle for each of the seven dosage regimens. The greater experience with regimens C, P, and R is due to the fact that regimen R was continued after study on the other regimens was stopped. Cycle control on all regimens was excellent, with an average cycle length of 28 days. The average number of days of flow (about 3.5 days) was almost identical for all regimens.

*Trademark of Ortho Pharmaceutical Corporation.

Table III. Fitted and actual data

	Stabilized spotting and BTB (%)		*First-cycle gastrointestinal disturbance (%)*		*Life-table pregnancy rate (7 mo.)*	
Regimen	*Actual*	*Fitted*	*Actual*	*Fitted*	*Actual*	*Fitted*
A	15.3	15.1	10.0	10.9	1.04	1.07
B	10.1	10.8	22.2	23.8	0.43*	0.44
C, P, R	12.2	12.0	15.7	14.7	0.69	0.67
H	16.5	12.7	25.8	29.1	0.52*	0.51
G	8.5	8.9	5.2	6.0	7.50	7.14
O	27.5	22.8	9.8	11.1	2.10	2.42
T	17.8	17.8	6.9	9.3	5.71	3.13

*Empiric adjustment to avoid nonzero pregnancy rates. See "Material and methods."

Since hormonal contraceptive treatment initially may cause slight physiologic changes, which later disappear or stabilize to some degree, the total cycle per cent of spotting and BTB in a study may be highly influenced by the amount of initial physiologic change and the average number of cycles per patient. Therefore, for purposes of comparing several dosage regimens, an estimate of the cycle per cent of spotting and BTB in the stabilized region would be more appropriate than the total cycle per cent. Estimates of the stabilized cycle per cent of spotting and BTB are presented by regimen in Table III.

The per cent of patients experiencing gastrointestinal disturbance during the first treatment cycle is also presented in Table III by regimen. Since the percentage of patients experiencing gastrointestinal disturbance after cycle one was very small in all seven regimens, it was thought that the first cycle per cent was appropriate for comparison between regimens.

Seven-month life-table estimates of the pregnancy rates per 100 women are shown in Table III. Seven-month rates were used since some regimens only had seven months of data available at the time of the analysis. Two of the regimens (B and H) studied had no observed pregnancies. In order to fit a response surface relating the life-table pregnancy rates to the dosage of the product, it was desirable to use only nonzero pregnancy rates (so that standard errors could be computed). To accomplish this, an empiric adjustment was made, similar to that proposed by Berkson,[15] in calculating the life-table rates for regimens B and H. These empiric pregnancy rates were 0.43 and 0.52, respectively.

Figs. 1 to 3 show three-dimensional representations

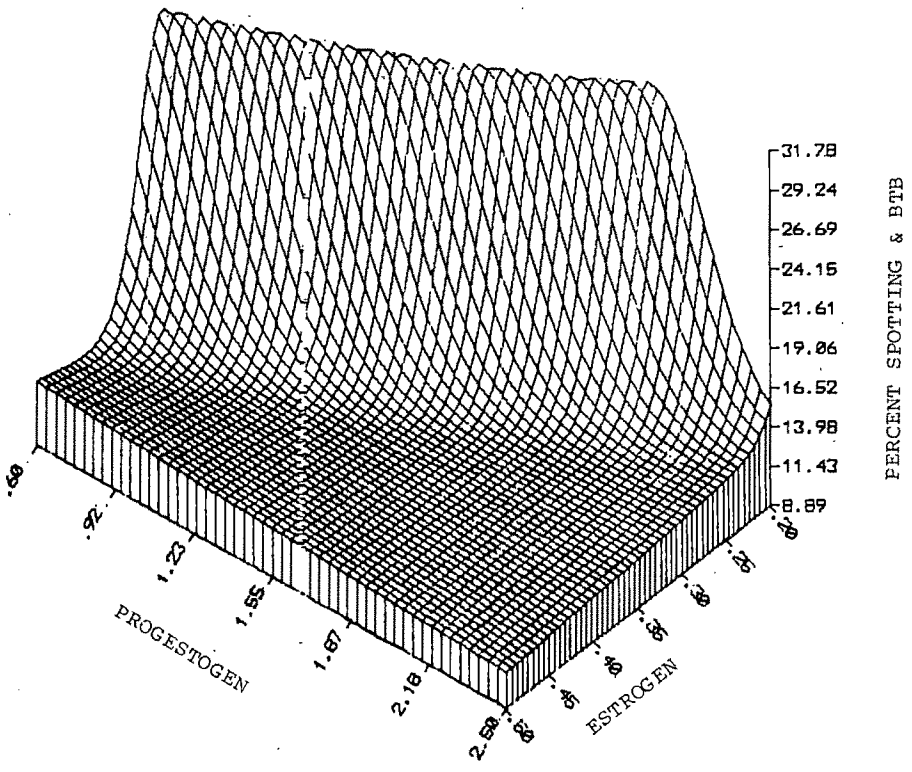


Fig. 1. Response surface for spotting and BTB combined.

of the fitted response surfaces for spotting and BTB, pregnancy rate, and per cent of gastrointestinal disturbance, respectively. Table III compares the fitted values (from the surfaces) to the observed values, and it can be seen that the fitted surface predicts the actual data rather well. The fitted values may be more reliable than the actual data since they combine the information from all the regimens in a cohesive manner. The response surfaces may also be used to predict the characteristics of dosage combinations not actually studied but still within the limits examined. Table IV, a semigraphic table, presents predictions for various alternate doses. It can be seen that slight reductions in either the progestin or estrogen doses from their levels in the C, P, and R regimens (i.e., 0.125/0.035) will significantly increase the amount of spotting or BTB and pregnancy rate.

Increasing the dose does not bring about a corresponding reduction in side effects or pregnancy rate. For this reason, the R regimen (0.125/0.035) was chosen as the optimal dosage of norgestimate and EE to be used in Phase III studies.

Comment

Examination of the response surface for spotting and BTB reveals that the amount of spotting and BTB is influenced, as others have reported, by the ratio of progestin and estrogen (i.e., more spotting and BTB at 0.060/0.050 and 0.250/0.020 than at 0.250/0.050). However, the major factor that seems to influence spotting and BTB in the low dose range is the absolute dose. As the dose of both estrogen and progestin is decreased, a much greater increase in spotting and BTB is observed than that produced by changing the ratio of the two components at higher doses.

The response surface for pregnancy rate shows that as the absolute dose of estrogen and progestin is reduced the pregnancy rate will increase in a smooth fashion. The upward twisting of the right side of the surface in the low-dose range indicates that the pregnancy rate is influenced more by the estrogen dose than by the progestin dose in low-dose combinations.

The low incidence of spotting and BTB for the lowest-dose combination (0.060/0.020) is difficult to explain; however, since there is a high pregnancy rate for that combination, it might be conjectured that this dosage was too low to prevent ovulation or provide sufficient exogenous estrogen to cause significant structural changes in the endometrium. The response surface for gastrointestinal disturbance clearly indicates that this side effect is almost totally estrogenically induced.

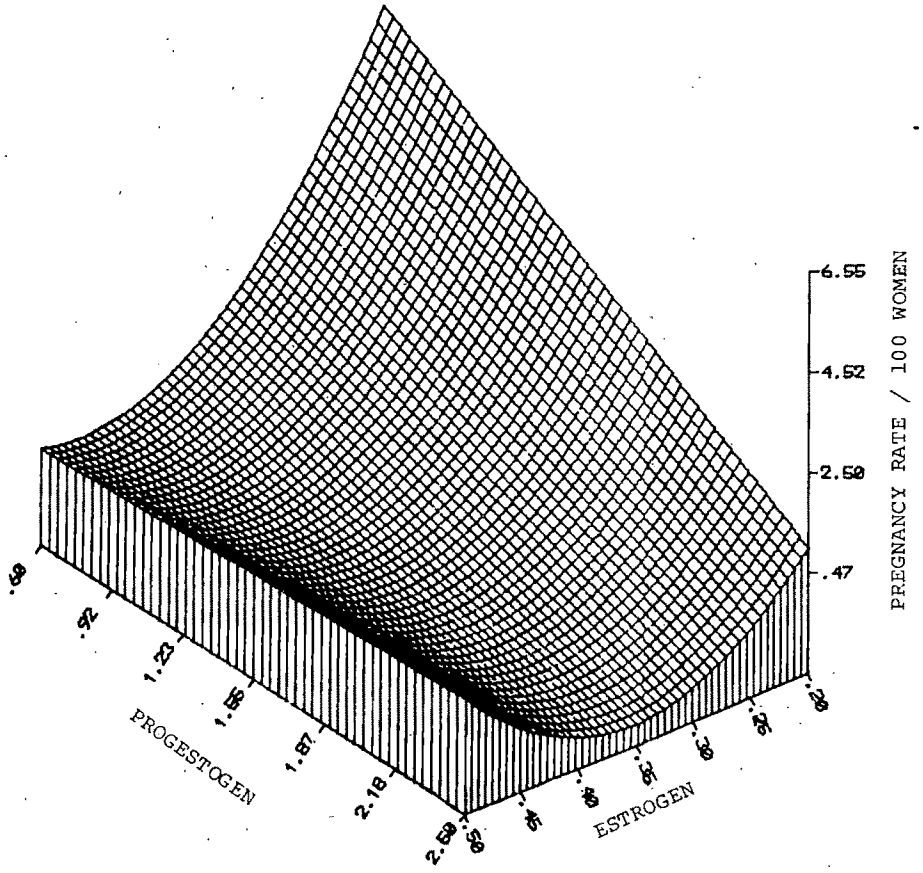


Fig. 2. Response surface for seven month pregnancy rate.

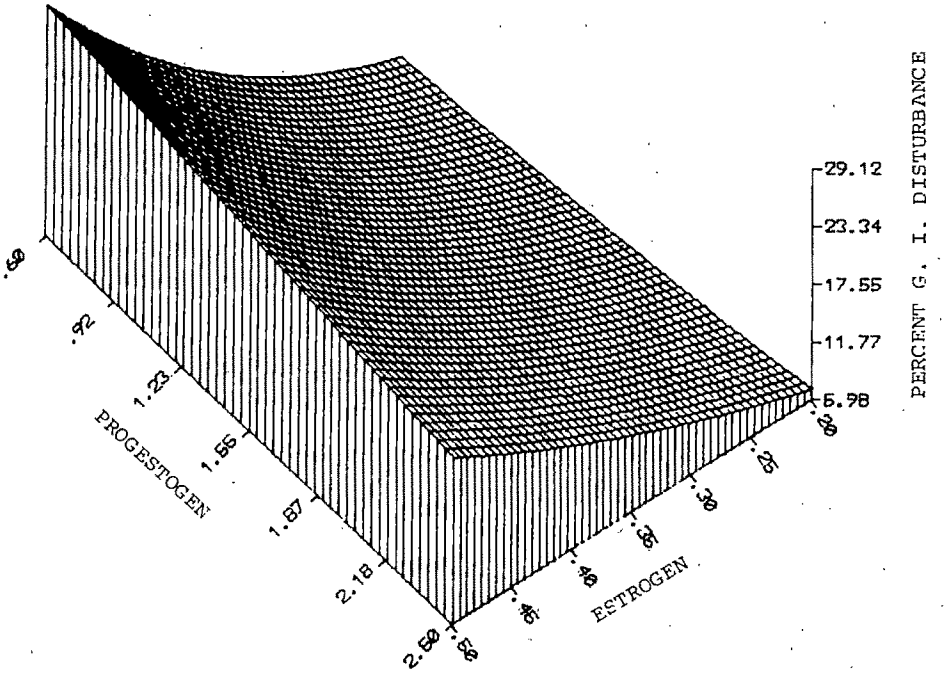


Fig. 3. Response surface for gastrointestinal disturbance.

Table IV. Effects of dosage changes (predicted values)

Effect	*Range*	*Differing estrogen dose*			*Differing progestin dose*		
		0.125/0.025	*0.125/0.035*	*0.125/0.045*	*0.100/0.035*	*0.125/0.035*	*0.150/0.035*
Pregnancy rate (7 mo.)	2.0-5.00	3.2					
	1.0-1.99				1.2		
	0.0-0.99		0.67	0.45		0.67	0.50
Spotting and BTB	14.1-20.0	17.8			18.2		
	12.6-14.0						
	10.0-12.5		12.0	11.5		12.0	11.4
Gastrointestinal disturbance	15.1-25.0			22.4			
	10.1-15.0		14.7		14.4	14.7	15.0
	0.0-10.0	9.3					

Simultaneous consideration of all three response surfaces has clearly indicated that the 0.125/0.035 dosage combination is minimal in some respects. Further reduction of either estrogen or progestin, with the other component unchanged, would be expected to result in an increased pregnancy rate and intermenstrual bleeding. The estrogen dose could be reduced without seriously changing the characteristics of the contraceptive by increasing the dose of progestin. For example, a 0.180/0.030 combination would probably be reasonable. On the other hand, the progestin dose could be reduced by increasing the estrogen dose and a 0.090/0.040 combination would probably have comparable characteristics in the same population of women.

In summary, it is believed that the examination of several appropriately selected dose regimens and the fitting of response surfaces to the observed efficacy and side-effect indicators has clarified the relationship between dosage, efficacy, and safety of a potential combination oral contraceptive containing 0.125 mg. of norgestimate and 0.035 mg. of EE, thus making the choice of an optimal dosage easier.

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Ovum transport in women treated with methyl ergonovine

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The location of ova in the genital tract was studied between 24 and 120 hours after the luteinizing hormone (LH) surge in 32 women who had been treated with methyl ergonovine in doses known to stimulate tubal contractility. Thirteen eggs were found in the fallopian tubes, between 48 and 120 hours after the LH peak, and no eggs were recovered from the endometrial cavity. No significant difference in tubal ovum recovery or in tubal segmental distribution of ova was found in comparison with these parameters in an untreated control group. These results indicate that stimulation of tubal contractility with methyl ergonovine does not accelerate ovum transport through the fallopian tubes in the human. (AM. J. OBSTET. GYNECOL. 134:321, 1979.)

A NUMBER OF drugs can modify tubal contractility in the human as shown by intraluminal pressure recordings. In previous work[1] we have shown that methyl ergonovine can induce long-lasting tubal contractions. After a single dose of 0.2 mg intramuscularly, a latency period of 90 to 120 seconds is followed by hypercontractility which lasts for nearly 4 hours. A clear dose-response relationship was also demonstrated.

Recent information[2] indicates that unfertilized ova in women reach the uterine cavity around 80 hours following ovulation. It is generally believed that ovum transport is accomplished by the mechanical interaction of tubal smooth muscle and ciliary activity. Therefore, it is logical to assume that the rate of ovum transport can be modified by drugs which stimulate tubal contractility.

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The purpose of this study was to determine whether or not the increased tubal contractility induced by methyl ergonovine results in accelerated passage of the ovum through the fallopian tubes.

Material and methods

This study included 50 healthy, fertile women, without contraceptive treatment during the month preceding the cycle studied. These women had been accepted for surgical sterilization by the Ethics Committee of the Department of Obstetrics and Gynecology of the J. J. Aguirre Hospital.* Each subject underwent a careful study of her obstetric and medical history and was given information on the nature and purpose of this study. Informed consent was obtained prior to admission to the study. All subjects were instructed to avoid intercourse during the study cycle, and this was controlled by daily examination of cervical mucus.

Blood was drawn daily between 9 and 10 A.M. starting 6 days before the expected day of ovulation until the day of operation and immediately assayed for es-

*The investigators from the Pontificia Universidad Católica de Chile do not belong to this Committee and had no participation in the clinical aspect, in the selection of patients, or in the surgical sterilizations which were done in J. J. Aguirre Hospital.

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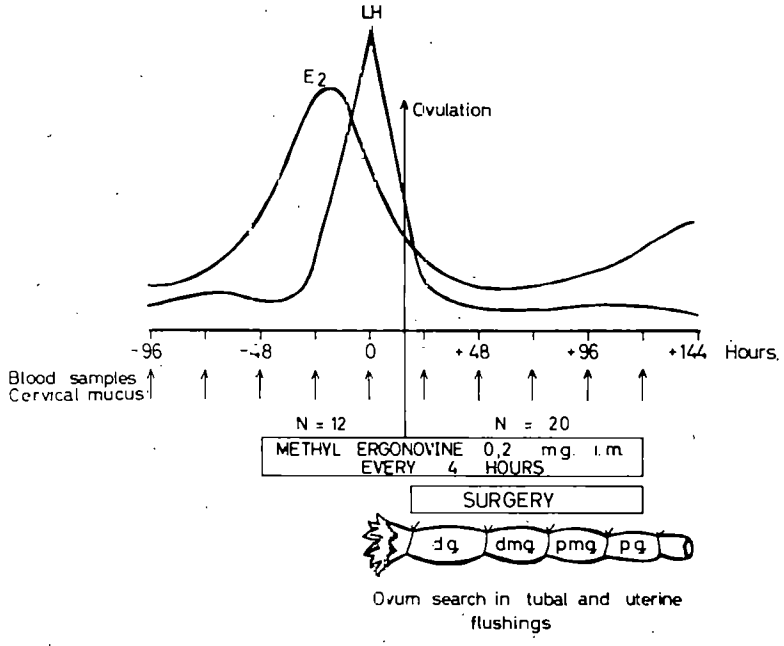


Fig. 1. Schematic drawing of the experimental design.

Table I. Distribution of subjects according to timing of first injection and total number of injections

*Total No. of injections per subject**	*Timing of first injection (hr. from LH peak)*			
	−24 to 0 hr. (No. of subjects)	*+1 to +24 hr. (No. of subjects)*	*+25 to +48 hr. (No. of subjects)*	*+49 to +72 hr. (No. of subjects)*
3-6	—	—	—	2
7-12	1	4	9	4
13-18	3	3	3	—
19-24	1	—	2	—

*Methyl ergonovine, 0.2 mg i.m. every 4 hours.

Table II. Ovum recovery from fallopian tube and endometrial cavity at different intervals following LH peak, in control[2] and treated groups

Hours from LH peak to operation	*Control*				*Treated*			
	Tube		*Uterus*		*Tube*		*Uterus*	
	(No. of eggs)	*(No. of cases)*	*(No. of eggs)*	*(No. of cases)*	*(No. of eggs)*	*(No. of cases)*	*(No. of eggs)*	*(No. of cases)*
24	2	4	0	3	0	1	0	1
48	1	6	0	5	3	7	0	7
72	11	19	0	17	7	9	0	8
96	5	13	1	12	2	11	0	10
120	0	6	2	3	1	4	0	3
144	0	6	2	5	-	-	-	-

trogen content by a rapid radioimmunoassay.[3] The preovulatory estrogen peak was used to time drug administration and operation. The remaining plasma was stored at −20° C for subsequent radioimmunoassay of luteinizing hormone (LH) and progesterone. Methyl ergonovine, 0.2 mg intramuscularly, was administered every 4 hours. The initiation of treatment in relation to LH peak and the number of injections given are shown in Table I.

In all cases operation was performed with spinal anesthesia between 24 and 120 hours following the LH surge and included the following steps: (1) laparotomy; (2) inspection of ovaries, to determine if ovulation had occurred, the ovulatory side, and the number of rup-

tured follicles; (3) placement of five ligatures along the tube to divide the lumen in four equal segments and prevent major displacement of the ovum during further manipulation of the organ; (4) salpingectomy; (5) removal or ligation and sectioning of the contralateral tube; (6) transfundal flushing of the endometrial cavity.

The tubes were sectioned at the site of each ligature and each segment was flushed separately with Tyrode's solution. All flushings were distributed in embryologic culture dishes and examined at low magnification to search for eggs. When the ovum was recovered the interval between the LH peak and recovery was expressed in multiples of 24 hours. LH was measured as described in Midgley.*[4] Progesterone was measured by radioimmunoassays, as described by Thorneycroft and Stone.[5]

A schematic drawing of the experimental design is shown in Fig. 1.

The results obtained in women treated with methyl ergonovine were compared with those of a control group previously reported.[2]

Results

Eighteen patients were eliminated from the study for the following reasons: anovulatory cycles, anatomic alterations of internal genitals, or presence of preovulatory follicles at the time of operation. In the 32 remaining patients the presence of a corpus luteum was confirmed macroscopically and microscopically.

As shown in Table I and Fig. 1 treatment with methyl ergonovine was initiated before ovulation in 12 patients and after ovulation in 20 patients. Ovulation was assumed to have occurred 17 hours following the LH peak, on the basis of previous observations.[6] In both groups the frequency of ovum recovery was similar; therefore, they were analyzed as a single group.

Ovum recovery according to the intervals between LH peak and operation and in comparison with a control group is shown in Table II. Thirteen ova were found in 32 treated subjects. All of them were recovered between 48 and 120 hours following LH peak and were located in the fallopian tube. The rate of ovum recovery from the fallopian tubes between 24 and 120 hours was 40.6% in the treated group and 39.6% in the control group.

The distribution of ova in the four tubal segments studied is shown in Fig. 2. In the control group there was a marked tendency of ova to be located in the middle quarters, regardless of time after LH peak.

*The reagents for measurement of LH were a gift from the National Institute of Arthritis, Metabolism and Digestive Diseases, National Pituitary Agency.

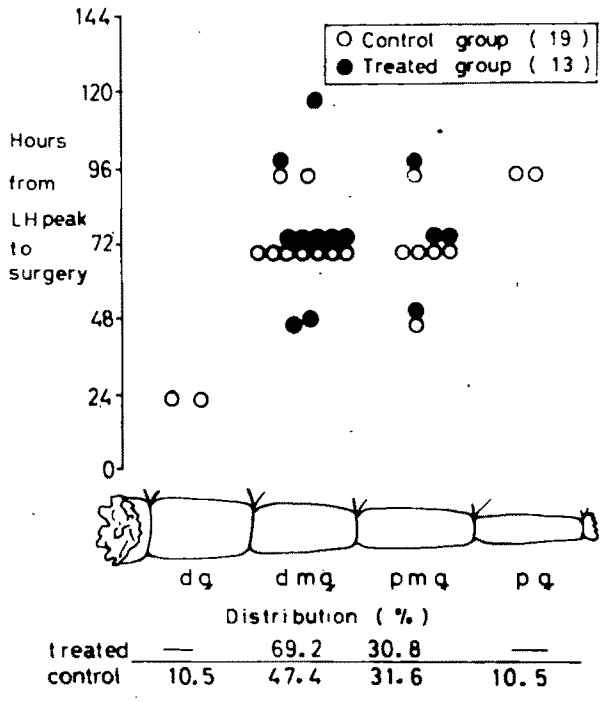


Fig. 2. Segmental distribution of ova in the fallopian tubes in control[2] and treated groups according to the time from LH peak to operation. *dq* = Distal quarter; *dmq* = distal middle quarter; *pmq* = proximal middle quarter; *pq* = proximal quarter.

Only 20% of ova were found in the extreme quarters. In the treated group all ova recovered were located in the middle quarters. The two distributions are not statistically different.

Comment

The purpose of this investigation was to assess the influence of increased tubal contractility produced by methyl ergonovine upon ovum transport through the fallopian tubes. The study was designed to test the hypothesis that increasing contractility could lead to accelerated passage of the ovum. This is reflected in the fact that ovum search was done in 28 of the 32 patients at a time when ova are normally found in the fallopian tubes. The comparison of ovum recovery from the tubes in treated and control subjects suggested that hypercontractility was not associated with premature passage of ova into the uterus. This was further substantiated by the fact that not a single ovum was recovered from the uterine cavity in 26 cases in which the cavity was flushed within the first 96 hours following the LH peak.

The distribution of ova among four tubal segments of the treated group was compared with that of a control group. This comparison showed that treatment

with methyl ergonovine failed to displace the ovum toward a more proximal position.

Contrary to our expectation the data presented clearly show that hypercontractility of the fallopian tubes induced by methyl ergonovine is not associated with acceleration of ovum transport.

The possibility of delayed passage of the ovum into the uterus as a consequence of treatment was not investigated in the present study since only four subjects were operated upon at a time when ova normally would have been recovered from the uterus.

The fact that ova were recovered from neither the tubes nor the uterus in three of those cases is within the method error but is compatible also with normal tubal transport followed by rapid expulsion from the uterus. This possibility should be kept in mind since methyl ergonovine at the doses given also stimulates contractility of the nonpregnant uterus.

The single ovum recovered from the fallopian tube 120 hours following the LH peak suggests that tubal locking of ova could be associated with hypercontractility.

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Effect of dexamethasone on gonadotropin responsiveness to luteinizing hormone–releasing hormone and clomiphene in women with secondary amenorrhea

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We have studied the effects of administration of dexamethasone, 2 mg orally every 6 hours, for 5 days on the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) induced by luteinizing hormone–releasing hormone (LHRH) in six women with secondary amenorrhea and on the release of these gonadotropins induced by clomiphene citrate in 10 women with secondary amenorrhea. Dexamethasone suppressed baseline serum levels of LH and FSH and blunted the LHRH-induced release of LH and FSH in six women. Following dexamethasone administration, the LH and FSH response to clomiphene citrate, which competes for gonadal steroid receptor binding sites in the hypothalamus, resulting in increased release of LHRH, was blunted in the 10 women studied. The data indicate that short-term administration of pharmacologic doses of glucocorticoids suppresses the secretion of LH and FSH by a direct effect on the anterior pituitary and possibly by an effect at the suprahypophyseal level with inhibition of release of LHRH. (AM. J. OBSTET. GYNECOL. 134:325, 1979.)

IT HAS BEEN PREVIOUSLY observed that women experience disorders of menstruation when receiving glucocorticoids.[1] Evidence from animal studies suggests that the suppressive effects of glucocorticoids on the hypothalamic-pituitary axis are exerted by impairment of gonadotropin secretion by a direct action on the anterior pituitary or by their effects at the suprahypophyseal level with inhibition of release of luteinizing hormone–releasing hormone (LHRH).[2–4] One prior report indicated that short term administration of dexamethasone did not result in suppression of basal levels of follicle-stimulating hormone (FSH) in man.[5] Long-term administration of glucocorticoids has been shown to suppress basal and midcycle luteinizing hormone (LH) peak levels in normally cycling women[6] and to suppress the LH response to LHRH in women with disorders of menstruation.[1]

The present study was performed to determine the effects of short-term administration of high doses of glucocorticoids on LH and FSH responses to LHRH and clomiphene in women with secondary amenorrhea.

Material and methods

Sixteen women (aged 21 to 37 years) with secondary amenorrhea and infertility were studied. The subjects had normal serum prolactin levels, normal lateral skull films, and normal visual fields and none had galactorrhea. Most of these patients were obese; they had high normal LH and normal FSH levels and slightly elevated serum testosterone and urinary 17-ketosteroid levels. The diagnosis of polycystic ovary disease was confirmed at laporoscopy in four of the subjects.

LHRH studies. Six women (aged 23 to 37) were given an intravenous bolus of 100 μg of LHRH at 0800 hours before and after they received dexamethasone, 2

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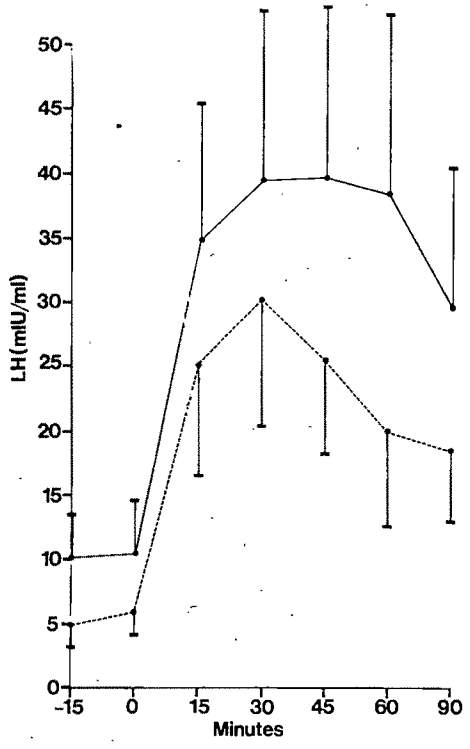


Fig. 1. Mean serum LH responses to LHRH (given at 0 time) in six women with secondary amenorrhea before (solid line) and after (broken line) dexamethasone administration; vertical bars show standard errors of the means.

mg orally every 6 hours for 5 days. Baseline samples of blood (−15 and 0 minutes) were drawn through an indwelling 19 gauge needle and further blood samples were obtained at 15, 30, 45, 60, and 90 minutes after injection of LHRH.

Clomiphene studies. Ten of the subjects (aged 21 to 34) were given 100 mg of clomiphene citrate orally for 5 days. Two weeks later the subjects received 100 mg of clomiphene citrate daily with simultaneous administration of dexamethasone, 2 mg orally every 6 hours for 5 days. On each occasion three blood samples were drawn at 0800, 0900, and 1000 hours prior to (day 1) and after (day 6) clomiphene citrate administration.

Radioimmunoassays. Serum was stored at −20° C and all LH and FSH samples from each study were measured in duplicate in one assay to avoid interassay variation. Serum levels of LH and FSH were measured by double-antibody radioimmunoassays; human antipituitary preparation LE-907 supplied by the National Pituitary Agency was used as the assay standard.[7] The lower limits of sensitivity were 1.0 mIU/ml for LH and 0.5 mIU/ml for FSH. The within-assay coefficients of variation were 5.1% for LH and 4.9% for FSH.

Statistics. Statistical comparisons of serum hormone

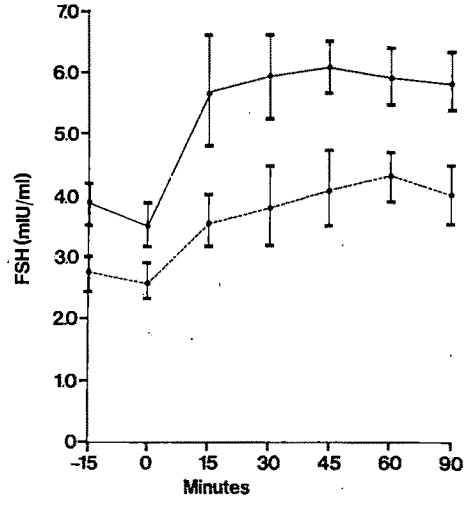


Fig. 2. Mean serum FSH responses to LHRH (given at 0 time) in six women with secondary amenorrhea before (solid line) and after (broken line) dexamethasone administration; vertical bars show standard errors of the means.

responses to LHRH and clomiphene before and after dexamethasone administration were made with Student's paired t test.

Results

The average basal (mean of −15 and 0 values) serum LH level for the six women receiving LHRH was significantly less ($p < 0.025$) after administration of dexamethasone (5.5 ± 2.5 mIU/ml) than with no pretreatment (10.2 ± 3.7 mIU/ml) (Fig. 1). The mean serum LH response to LHRH in the six women after dexamethasone was less ($p < 0.05$) at the sampling times of 15, 45, 60, and 90 minutes after LHRH administration than the response with no dexamethasone pretreatment (Fig. 1). Dexamethasone administration resulted in a reduction ($p < 0.01$) in the average basal serum FSH value from 3.7 ± 0.3 mIU/ml to 2.7 ± 0.3 mIU/ml (Fig. 2). The FSH response to LHRH in these six women was less ($p < 0.005$) after dexamethasone pretreatment at all sampling times from 15 through 90 minutes after LHRH administration.

Table I shows that administration of dexamethasone in 10 subjects resulted in a reduction ($p < 0.01$) in the incremental LH and FSH responses to clomiphene citrate.

Comment

In this study basal levels of LH and FSH were clearly lowered by short-term administration of high doses of dexamethasone, which is in agreement with a previous observation in young women[6] and which differs from

Table I. Mean (± standard error of the mean) responses of LH and FSH in 10 women after oral administration of 100 mg of clomiphene citrate daily for 5 days

	Baseline LH (mIU/ml)	*Baseline FSH (mIU/ml)*	*LH after clomiphene (mIU/ml)*	*FSH after clomiphene (mIU/ml)*	*δ LH (mIU/ml)*	*δ FSH (mIU/ml)*
No dexamethasone	5.0 ± 0.7	2.7 ± 0.5	8.8 ± 1.4	4.0 ± 0.6	3.8 ± 0.8	1.2 ± 0.2
With dexamethasone	4.9 ± 0.7	2.7 ± 0.4	5.9 ± 1.2	3.3 ± 0.5	1.1* ± 0.6	0.6* ± 0.1

*Significant difference in the response to clomiphene during oral dexamethasone (2 mg every 6 hours) compared to the response in the absence of dexamethasone administration.

the previous report of no suppression by glucocorticoids of FSH levels in young men.[5] These observed differences in the effects of glucocorticoids on basal LH and FSH secretion are probably related to dose and duration of administration and to sexually related differences in sensitivity to glucocorticoid suppression. Sowers and co-workers[8] have previously shown that short-term high-dose dexamethasone administration suppresses basal thyroid-stimulating hormone (TSH) and prolactin (PRL) secretion in man. The results of these studies may indicate that pharmacologic doses of glucocorticoids exert a general inhibitory effect on the basal secretion of anterior pituitary hormones.

The observation in this study that short-term administration of high doses of dexamethasone suppresses the LH and FSH response to LHRH and clomiphene is consistent with prior observations in women receiving long-term glucocorticoid therapy.[1] The findings in these studies indicate a direct inhibitory effect of glucocorticoids at the level of the anterior pituitary. Clomiphene citrate stimulates gonadotropin secretion, probably by competing for gonadal steroid binding sites in the hypothalamus, thus blocking the negative feedback action of estrogen on LHRH secretion.[9] Our observation that dexamethasone administration inhibits the LH and FSH response to clomiphene suggests that glucocorticoids may also act at the level of the hypothalamus to inhibit the release of LHRH. In support of this concept is the previous observation that cortisol implants in the medial basal hypothalamus in immature rats delay sexual maturation,[10] suggesting an action of glucocorticoids at the suprahypophyseal level. However, the blunted gonadotropin response to clomiphene that we observed could also represent direct inhibition by glucocorticoids at the level of the anterior pituitary.

In man glucocorticoids exert suppressive effects at the hypothalamic-pituitary level not specific to the adrenocorticotropic axis. Glucocorticoids suppress hypoglycemia-induced growth hormone release,[11, 12] eliminate the periodicity of TSH secretion,[13] and blunt the TSH and PRL response to thyrotropin-releasing hormone.[8, 14, 15] We further observed that glucocorticoids lower basal secretion of LH and FSH and blunt the gonadotropin response to LHRH and clomiphene in women with disorders of menstruation. However, these observations may not be applicable to women with normal menstrual cycles.

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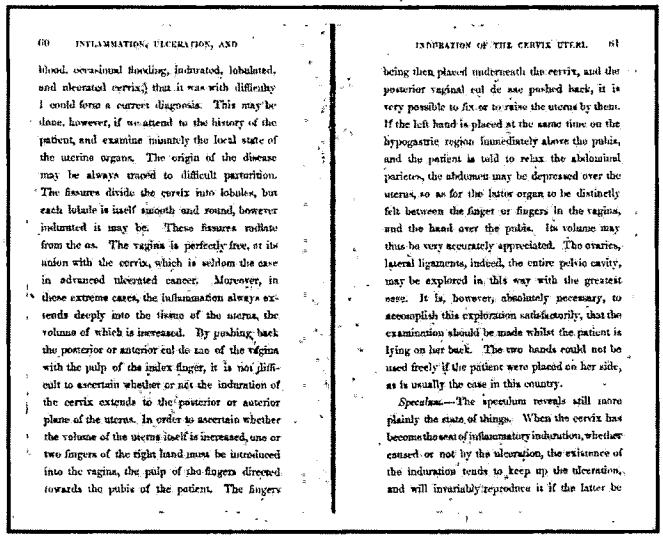
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JAMES HENRY BENNET
London, John Churchill, 1845



60 INFLAMMATION, ULCERATION, AND

blood, occasional flooding, indurated, lobulated, and ulcerated cervix; that it was with difficulty I could form a correct diagnosis. This may be done, however, if we attend to the history of the patient, and examine minutely the local state of the uterine organs. The origin of the disease may be always traced to difficult parturition. The fissures divide the cervix into lobules, but each lobule is itself smooth and round, however indurated it may be. These fissures radiate from the os. The vagina is perfectly free, at its union with the cervix, which is seldom the case in advanced ulcerated cancer. Moreover, in these extreme cases, the inflammation always extends deeply into the tissue of the uterus, the volume of which is increased. By pushing back the posterior or anterior cul de sac of the vagina with the pulp of the index finger, it is not difficult to ascertain whether or not the induration of the cervix extends to the posterior or anterior plane of the uterus. In order to ascertain whether the volume of the uterus itself is increased, one or two fingers of the right hand must be introduced into the vagina, the pulp of the fingers directed towards the pubis of the patient. The fingers

INDURATION OF THE CERVIX UTERI. 61

being then placed underneath the cervix, and the posterior vaginal cul de sac pushed back, it is very possible to fix or to raise the uterus by them. If the left hand is placed at the same time on the hypogastric region immediately above the pubis, and the patient is told to relax the abdominal parietes, the abdomen may be depressed over the uterus, so as for the latter organ to be distinctly felt between the finger or fingers in the vagina, and the hand over the pubis. Its volume may thus be very accurately appreciated. The ovaries, lateral ligaments, indeed, the entire pelvic cavity, may be explored in this way with the greatest ease. It is, however, absolutely necessary, to accomplish this exploration satisfactorily, that the examination should be made whilst the patient is lying on her back. The two hands could not be used freely if the patient were placed on her side, as is usually the case in this country.

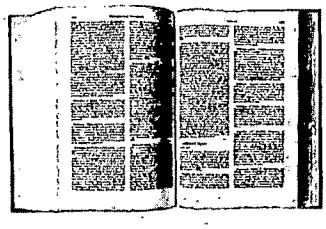
Speculum.—The speculum reveals still more plainly the state of things. When the cervix has become the seat of inflammatory induration, whether caused or not by the ulceration, the existence of the induration tends to keep up the ulceration, and will invariably reproduce it if the latter be

Until the advent of cellular pathology the differentiation between benign and malignant uterine tumors presented a vexing problem for physicians who used the term "mole" for both until the mid–nineteenth century. Bennet, of London, first presented criteria to distinguish clearly between malignant and nonmalignant uterine neoplasms. His treatise was based on his seven years' experience as pupil and later "intern" and "resident medical functionary" in the hospitals of Paris and primarily was concerned with inflammation and ulceration of the uterine cervix. He wrote in the preface: "... I was compelled to analyze carefully the morbid phenomena of every case, so as to satisfy the inquiring disposition ... I was thus soon to perceive, that however carefully the field of uterine pathology had been investigated, there still remained much to be elucidated." During this period vaginal examination of women with uterine disorders was infrequently carried out, and it was Bennet, in England, who popularized the use of the speculum, which had been described by Joseph C. A. Récamier only a few years previously. Bennet described in great detail the normal cervix and

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its variants in both nonparous and parous women. "The size and length of the cervix uteri vary considerably in different females. Indeed, these physiological variations are so great, that were we to allow curselves to be guided by size alone . . . we should, undoubtedly, be often misled, and induced to suppose that disease existed when it did not." He maintained that leukorrhea was a result of inflammation of the cervix or endometrium "endometritis") rather than being a primary disease in itself. "If, however, a wide, thick stream of muco-pus issues deeply from between the lips, it probably originates in the uterine cavity, and the membrane which lines it is most likely inflamed." Bennet taught that infertility commonly resulted from inflammation and ulceration of the cervix. "In nearly all, and perhaps in all the cases which I have narrated, the females affected, although exposed to sexual intercourse, remained sterile during the entire duration of the disease; in some, a period of many years." He also observed that such inflammations were much more common in multiparous patients and, in fact, that "the state of pregnancy itself predisposes to such inflammation and ulceration . . ." In addition he also described syphilis of the cervix, a relatively uncommon lesion as compared with chancre of the vulva or vagina, and presented criteria for distinguishing this from other ulcerations. Bennet described the marked increase in blood supply to the uterus during pregnancy: ". . . the entire organ becomes one of the most instead of one of the least vascular in the human economy." The majority of Bennet's monograph treats the cervix and its diseases, both benign and malignant, and includes 18 case reports to illustrate his points. Perhaps one of his more important contributions was to distinguish by visual and tactical examination between benign and malignant disease of the cervix. In benign conditions: "the fissures divide the cervix into lobules, but each lobule is itself smooth and round, however indurated it may be . . .. The vagina is perfectly free, at its union with the cervix, which is seldom the case in advanced ulcerated cancer . . .." He continued by describing in detail various manifestations of cervical cancer, such as corroding ulcer, cauliflower excrescence, scirrhous form, and others. Bennet noted that it was not hardness of the cervix that distinguished cancer, ". . . but the irregularity of the hardened surface, and the existence of the tubercles, which project here and there," and confessed that "there are, nevertheless, instances in which the distinction is difficult to make, when the cervix has been deeply fissured by difficult labours or miscarriages . . .. In such instances, the indurated organ may be divided into several lobes, and present an uneven, and apparently irregular surface, although merely chronically inflamed. On a closer examination, however, it will be found that the fissures which separate the lobes radiate around the cavity of the os as a centre, which is not the case in cancerous tumors, and that each separate lobe is perfectly smooth in itself, and free from tubercle or superficial inequalities. If these data were generally known, and always kept in mind, errors of diagnosis in the first stage of the disease would seldom be made; but I believe that such is not the case, and that mere induration of the cervix, particularly if the organ is lobulated, is not infrequently taken for cancer, and treated as such. When this occurs, it is not surprising that the disease should give way under rational treatment, and that practitioners who fall into this error should conscientiously be able to bring forward cases to prove that they have cured incipient cancer . . .. When once ulceration has occurred, the diagnosis becomes much easier . . . there is generally loss of substance; the ulcerated surface is also hard, and presents numerous lobules, tubercles, hard ridges, disseminated with the utmost irregularity, and presenting, as a rule, that stony hardness which is only occasionally met with an inflammatory induration." He presented many treatments for the various benign cervical inflammations and ulcerations. Bennet's insistence that inflammation of the cervix was the prime uterine affection that led to associated problems, including prolapse, menstrual irregularities, parametritis, pelvic pain, bladder irritation, etc., and that these could be cured by local treatment of the cervix (including bleeding by leeches), led mid–nineteenth century gynecologists to a renewed attack on cervical disease with various caustics, tinctures, and emollients. Although a true distinction of malignant and nonmalignant cervical and uterine lesions had to await Rudolf Virchow, Bennet, by helping to differentiate benign from malignant uterine disease, made possible a rational surgical approach to uterine tumors. A second edition of Bennet's work, more than doubled in size, appeared in 1849, and this was followed by two subsequent English editions as well as translations into French and German. For many years Bennet served as one of the editors of the *Lancet*. Because of chronic pulmonary disease, he retired to the French Riviera where he continued to write, one of his important works being "Treatment of Pulmonary Consumption by Hygiene, Climate and Medicine."

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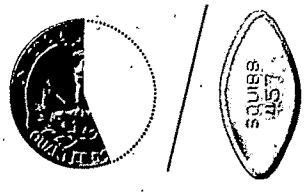
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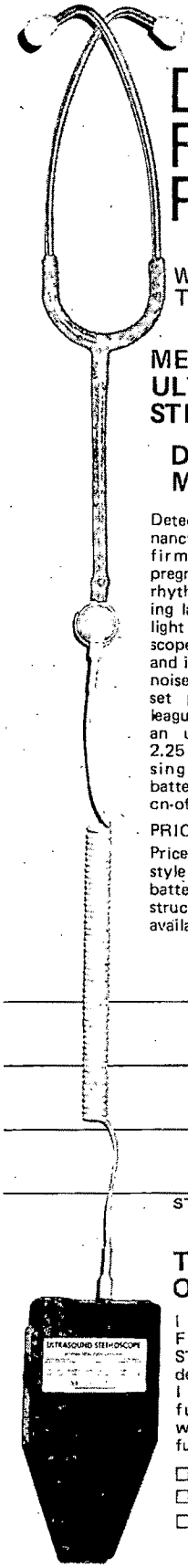
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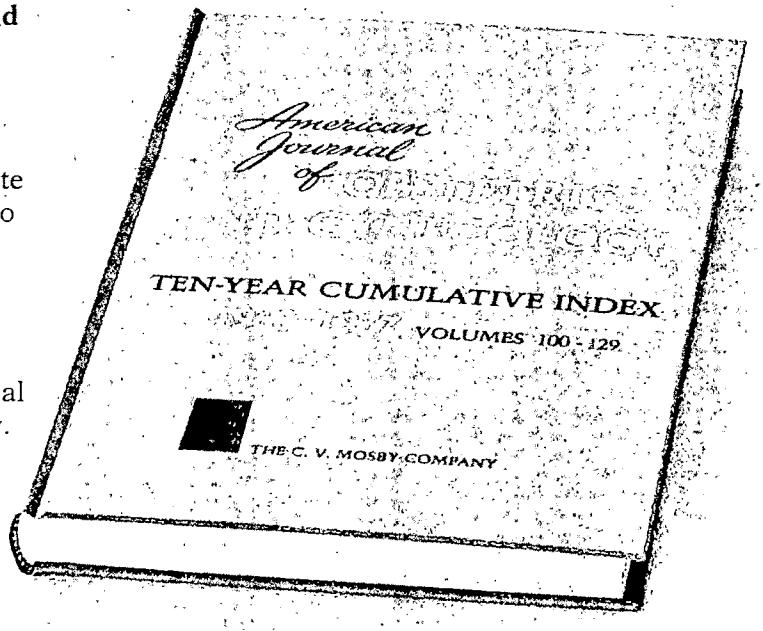
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CURRENT DEVELOPMENTS

Ultrasound in the diagnosis of congenital anomalies

JOHN C. HOBBINS, M.D.
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RICHARD L. BERKOWITZ, M.D.
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With high-resolution ultrasound equipment, it is now possible to diagnose certain fetal anomalies in the third trimester and in some cases before the twentieth week of gestation. During a 27 month period 2,548 ultrasound scans were performed in high-risk patients. An anomaly was diagnosed in 10 of 122 second-trimester patients who were at risk for recurrent fetal defects. Fetal deformity was also found in 26 third-trimester patients. Of the 2.8% of patients found to have polyhydramnios 18% were associated with various types of anomaly. With ultrasound it was possible to examine internal fetal anatomy and to identify abnormalities of the fetal cranium, spine, chest, abdomen, and limbs. These anomalies are reviewed here in detail. Based on ultrasonically derived information, second-trimester patients can be offered information concerning the status of their fetuses at risk genetically and physicians can better manage third-trimester patients with diagnosed fetal deformities. (AM. J. OBSTET. GYNECOL. 134:331, 1979.)

WITH THE IMPROVED sophistication of high-resolution gray-scale ultrasound equipment, it has become possible to better delineate fetal anatomy. This has enabled the ultrasonographer to identify some fetal anomalies which have previously eluded diagnosis. As a result, second-trimester patients who have already been delivered of infants with inherited defects can often be offered diagnostic information early enough to allow them the option of terminating the pregnancy. In the third trimester, pregnancies complicated by fetal anomaly are not terminated unless the condition is incompatible with extrauterine survival. However, ultrasonically derived information may be critical to the patient's obstetric management as well as the immediate care of the newborn infant. For these reasons, it is important that those responsible for the care of patients at risk for fetal anomalies are aware of the diagnostic potential of ultrasound, its advantages, and its limitations.

This report reviews our experience in the diagnosis of congenital anomalies in utero with ultrasound during the period from June, 1976, through August, 1978. Scanning was done in a total of 2,548 patients who either had various complications of pregnancy (Table I) or were at risk for fetal anomalies (Table II). Many of the patients studied were referred from locations outside our catchment area because of a high-risk pregnancy or suspicious findings at the referring institution.

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Nonspecific ultrasonic findings associated with fetal anomalies

Abnormalities of amniotic fluid volume. Many fetal anomalies are associated with either excessive or diminished amounts of amniotic fluid. The volume of this fluid increases linearly until the thirty-eighth week

Table I. Diagnosis of congenital anomalies made in the third trimester in patients studied during a 27 month period

Anomaly	*No.*
Hydrocephalus	5
Anencephaly	7
Intrathoracic cyst (enteric cyst)	1
Diaphragmatic hernia	1
Duodenal atresia	2
Multicystic kidney disease	2
Ureteral obstruction with cystic dysplastic kidney	1
Omphalocele	1
Thanatophoric dysplasia	1
Miscellaneous multiple anomalies	5
Total	26

Table II. Diagnosis of congenital anomalies in second trimester in patients genetically at risk for fetal deformity*

	Pregnancies examined (No.)	*Positive diagnoses (No.)*
Hydrocephalus	17	3
Neural tube defects (total of 82):		
Anencephaly in previous pregnancy	37	0
Spina bifida in previous pregnancy	41	1
Meningomyelocele in previous pregnancy	4	0
Polycystic kidney disease	4	2
Renal agenesis	2	0
Short limbed dysplasia	9	2
Fanconi's anemia	1	0
Roberts syndrome	4	2
Asphyxiant thoracic dysplasia	2	0
Thoracochondrodystrophy	1	0
Total	122	10

*Other anomalies described in text were not in those patients at risk genetically.

of gestation, at which time a mean volume of 1,000 cc is present.[2] After 38 weeks, the quantity of fluid diminishes progressively to about 250 cc at 43 weeks.[2] Well-defined limits of normalcy, however, have not been described. Precise determination of amniotic fluid volume is difficult and the only ultrasonic method reported, which derives this measurement by cross-sectional pelvimetry,[26] is beyond the constraints of most ultrasound laboratories. Calculation of total intrauterine volume (TIUV)[14] permits semiquantitative determination of this variable in the serial monitoring of a pregnancy. Although an abnormal TIUV is defined as being outside 95% confidence limits for a given gestational age, many pregnancies complicated by fetal anomaly are associated with lesser degrees of deviation from the mean.

Oligohydramnios. Oligohydramnios can be ultrasonically appreciated by noting a paucity of fluid in the area of the fetal arms and legs. This produces an impression of crowding (Fig. 1). The fetal kidney plays an important role in the formation of amniotic fluid. Oligohydramnios, therefore, strongly suggests fetal renal impairment in a pregnancy at risk for kidney abnormalities. This is particularly true when the reduction in amniotic fluid volume is noted before the twenty-eighth week of gestation. After this time, nonanomalous situations such as intrauterine growth retardation (IUGR), premature rupture of membranes (PROM), or postterm pregnancy may be responsible for oligohydramnios. The above conditions were responsible for oligohydramnios found in 7% of the patients studied.

Polyhydramnios. Amniotic fluid is in part cleared from the uterine cavity by fetal swallowing,[13] and conditions which compromise this function often result in polyhydramnios (Fig. 2). These conditions would include central nervous system abnormalities such as anencephaly and meningomyelocele. Obstruction to the fetal gastrointestinal tract proximal to the ileum is also consistently associated with polyhydramnios.[33] Since intrathoracic cysts and diaphragmatic hernias can be associated with polyhydramnios, it is likely that another cause of polyhydramnios is extrinsic pressure on the upper gastrointestinal tract.

Polyhydramnios is often noted in complications of pregnancy apart from fetal anomalies, such as Rh disease or diabetes. In many circumstances polyhydramnios occurs for no apparent reason, and in some cases the condition is not seen on repeat scan. During the study period, ultrasonically appreciated relative hydramnios (persisting on repeat scans) was diagnosed in 2.8% of pregnancies and anomalies were noted in 18% of these cases. This is in accord with a previous study suggesting a 20% chance of anomaly in polyhydramnios.[28] It is of interest that in an additional 22 cases polyhydramnios was diagnosed but was not evident on repeat examination.

Ascites. Ascites can be detected on transverse scanning by noting an echo-spared area surrounding the intraperitoneal contents (Fig. 3). This condition can be differentiated from a large intra-abdominal cyst by the uniformity of fluid accumulation in all quadrants of the abdomen. Fetal ascites occurs in a variety of conditions, such as urinary tract obstruction, chylous ascites, "prune belly" syndrome, and other multiple anomaly syndromes.[12] Although the exact etiology of fetal ascites is unknown, it has been postulated that the intra-

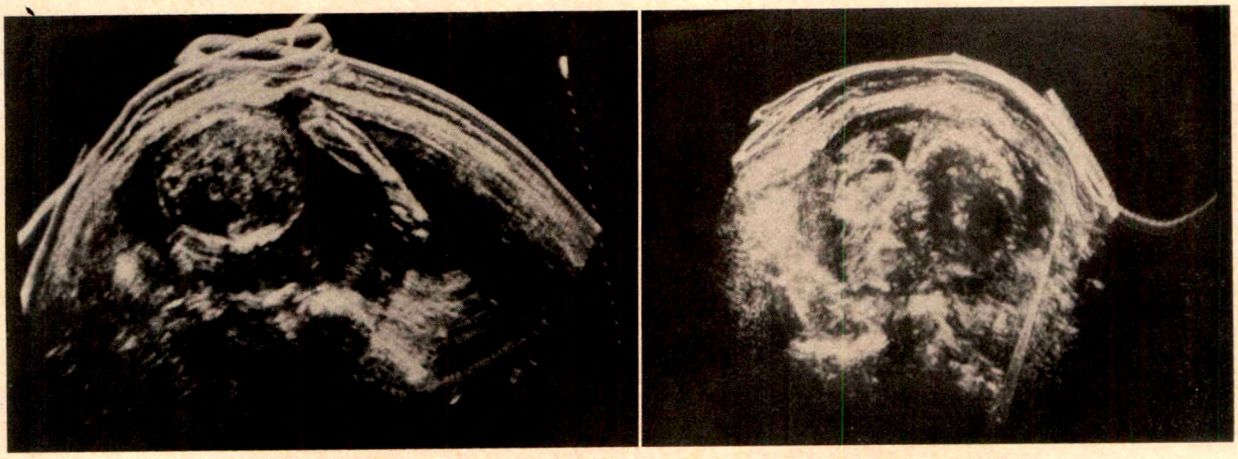


Fig. 1. Oligohydramnios. These transverse scans were obtained in two pregnancies of the same gestational age. There is marked crowding of the fetal small parts on the scan to the right. The uterine diameters are significantly smaller.

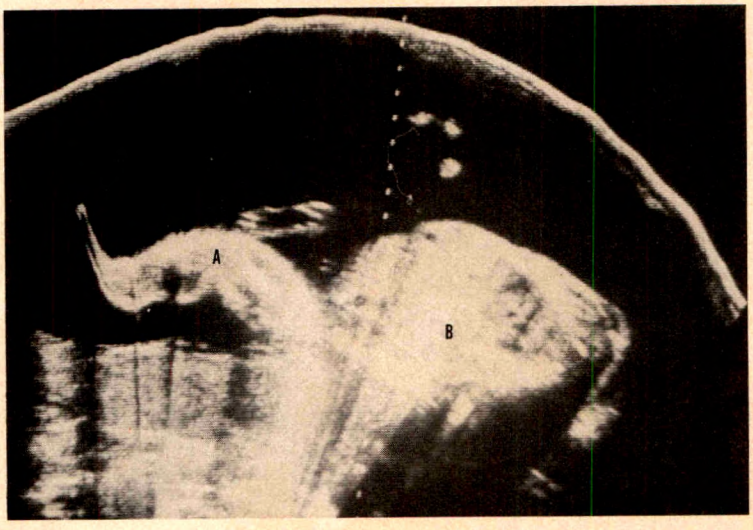


Fig. 2. Polyhydramnios. The ample black area represents excessive amniotic fluid. *A:* Leg; *B:* body.

peritoneal fluid accumulates as a result of heart failure, obstructed venous return, hypoproteinuria, or a combination of these. When fetal ascites is seen, the prognosis is ominous, although we are aware of two rare cases where infants have lived when the ascites was an isolated finding. During the study period, all five anomalous fetuses with ascites died either before delivery or within a few days following birth. One fetus, however, was delivered at 34 weeks after about 500 cc of ascitic fluid was removed from the fetal abdomen. The infant died of respiratory distress, and at autopsy the only abnormality found was fibrous bands in the peritoneal cavity.

Hydrops. It has been assumed that the generalized edema seen in fetal hydrops is secondary to cardiac failure. Validation of this concept, however, awaits studies of fetal cardiac function. Hydrops is manifested by abnormal thickening of the placenta (more than 5 cm) and a preponderance of low-level echoes within the placental substance. Subcutaneous edema is identified by increase in thickness of the scalp and abdominal wall. The liver is often enlarged, and ascites is a consistent feature. Although fetal hydrops is noted in severe erythroblastosis, generalized edema can also result from nonimmune causes. For instance, it was possible in one patient to diagnose alpha thalassemia at 22 weeks' gestation by the finding of gross placental hydrops. Amniotic fluid and fetal blood studies con-

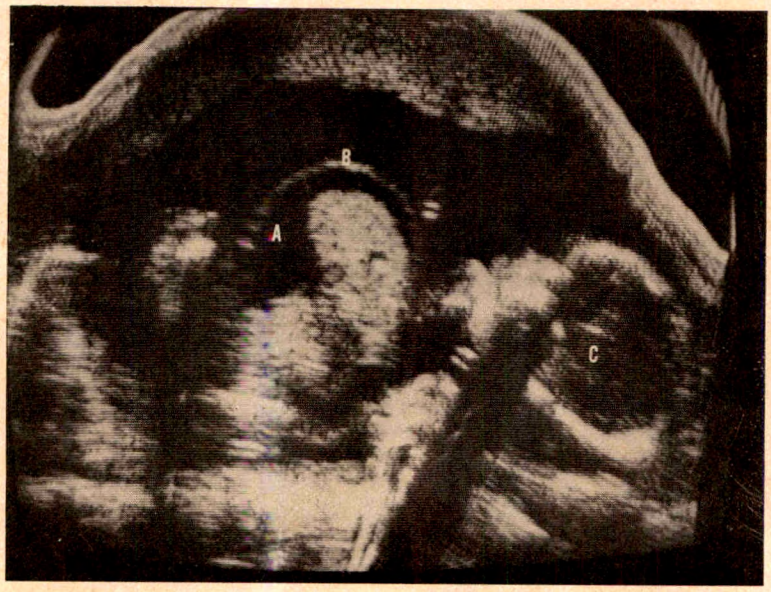


Fig. 3. Ascites is demonstrated in this scan of a fetus with multiple congenital anomalies. *A:* Ascites; *B:* body; *C:* head. (From Hobbins, J. C., and Winsberg, F.: Ultrasonography in Obstetrics and Gynecology, Baltimore, © 1977 by The Williams & Wilkins Co.)

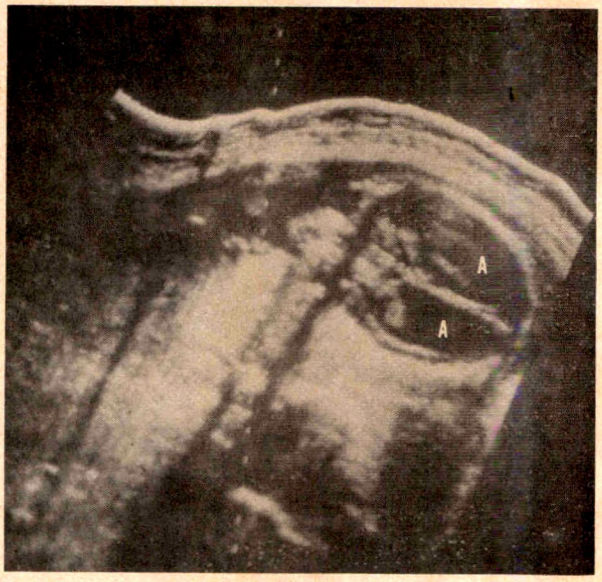


Fig. 4A. Hydrocephalus. Dilated lateral ventricles *(A)* in a hydrocephalic fetus at 20 weeks.

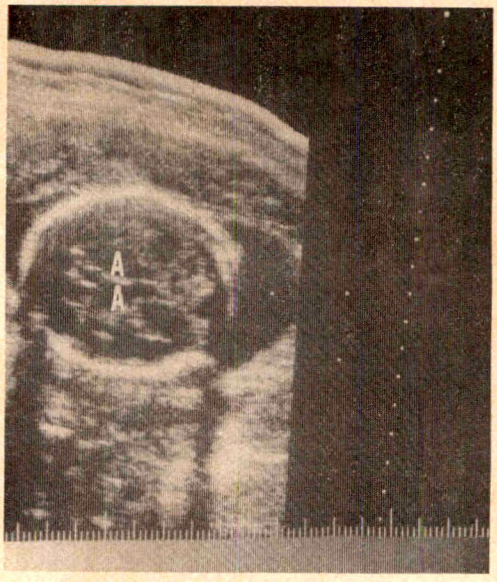


Fig. 4B. Normal lateral ventricles *(A)* at 19 weeks.

firmed the diagnosis. Fetal hydrops, whatever the cause, is associated with a grave prognosis.

Specific fetal areas

Cranium. Approximately 10% of major fetal anomalies involve the head and spine. Although abnormalities of the fetal cranium have been reported with ultrasound in the third trimester,[8, 11, 20, 25] most of these deformities can be identified in the second trimester.

Hydrocephalus. Recent investigation[3] has indicated that the lateral ventricles become abnormally dilated in hydrocephalus before there is a change in the outer skull outline. Therefore, scans in early pregnancy may reveal a normal biparietal diameter (BPD) and head circumference but show an extension of the lateral ventricles past a point which is midway between the falx and the outer skull outline (Fig. 4A). Under normal circumstances, the ventricles should not occupy this

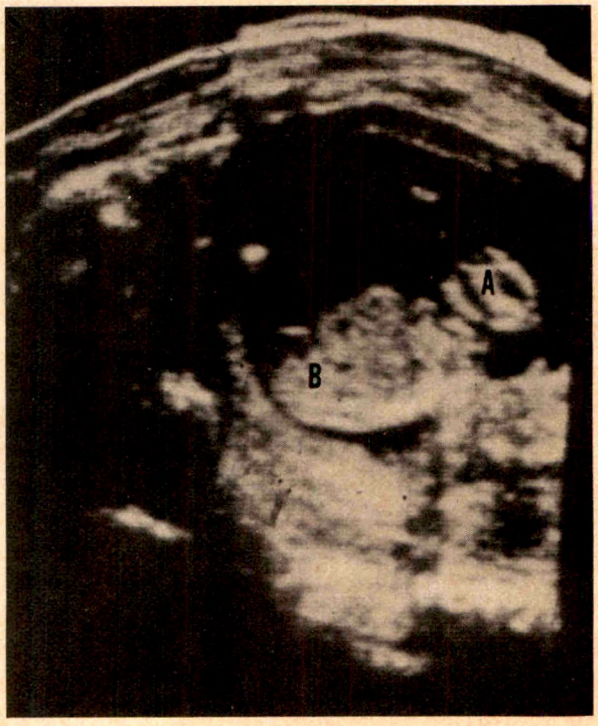


Fig. 5. Anencephaly. Facial structures are seen in this 15 week anencephalic fetus. The calvarium is absent. *A:* Face; *B:* body.

large an area after the seventeenth week of gestation (Fig. 4B). Failure to find dilated ventricles at this time does not exclude the development of hydrocephalus later in gestation, but preliminary experience suggests that this is not common.

In this series, scanning was done in the second trimester in eight patients who had been delivered of infants with communicating hydrocephalus (the most common form of the condition). In one of these cases, dilated lateral ventricles were noted. The pregnancy was terminated and the diagnosis confirmed at autopsy. In two other second-trimester patients not at recognized risk for fetal hydrocephalus, dilation of the lateral ventricles was diagnosed. One pregnancy was terminated (at which time the diagnosis was confirmed) and the other continued. In the latter case the BPD enlarged appropriately for gestation until the thirty-third week, after which the BPD increased by 2.7 cm in 4 weeks (mean normal growth, 1.5 cm). The infant was delivered at 37 weeks and lived only a few hours. Autopsy confirmed the diagnosis of hydrocephalus. In all of these cases of hydrocephalus, the BPDs were within one standard deviation of the mean for gestation before the twenty-fourth week.

Some forms of hydrocephalus have a higher recurrence risk than the empiric 1% to 4%.[29, 31] One of these

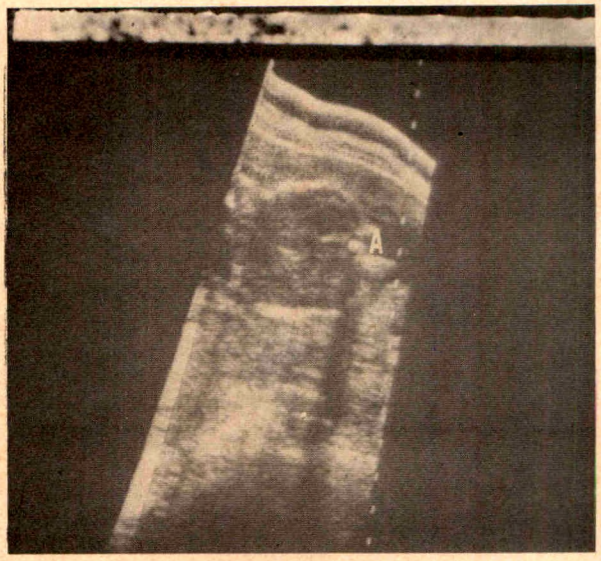


Fig. 6. Spina bifida. Defect in spinal column. Transverse scan at level of the first lumbar vertebra *(A)*.

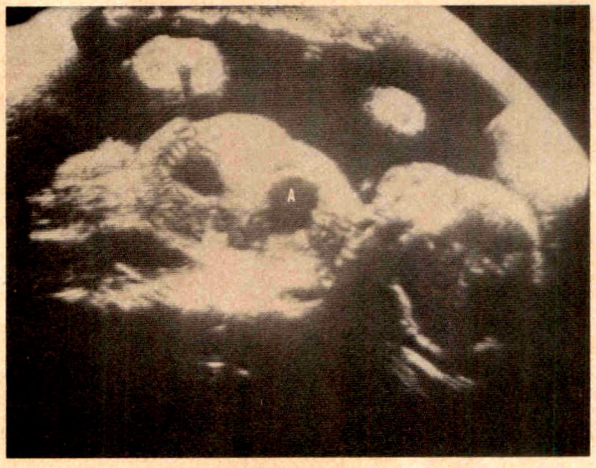


Fig. 7. Diaphragmatic hernia. This sagittal scan reveals an intrathoracic echo-spared area *(A)* adjacent to the heart, representing herniated abdominal contents.

is aqueductal stenosis, a block between the third and fourth ventricles. This condition may be secondary to hemorrhagic or inflammatory processes in the brain or may occur as an X-linked trait. The former etiologies probably represent acquired, nongenetic disease whereas the latter predicts familial recurrence in male offspring. X-linked aqueductal stenosis, inherited from the mother, has a 50% recurrence in male offspring and essentially no occurrence in female offspring. Accurate estimates of the genetic proportion of congenital aqueductal stenosis do not exist, but one writer[10] suggested that 2% of all cases of uncomplicated hydrocephalus have X-linked aqueductal stenosis. If

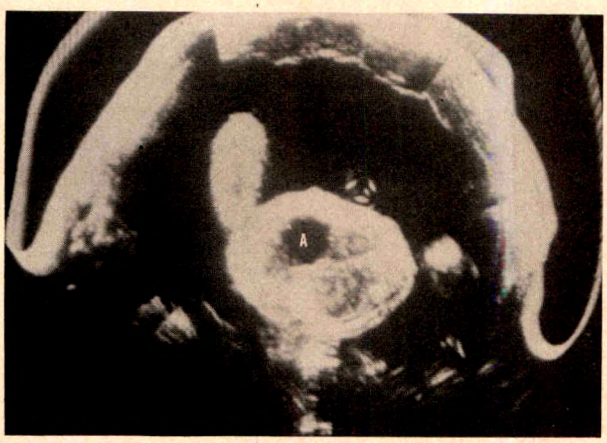


Fig. 8. Diaphragmatic hernia. A transverse scan at the level of the diaphragm demonstrates the defect *(A)*. (From Touloukian, R. J.: Intestinal atresia, Clin. Perinatol. 5:3, 1978, published by W. B. Saunders Co.)

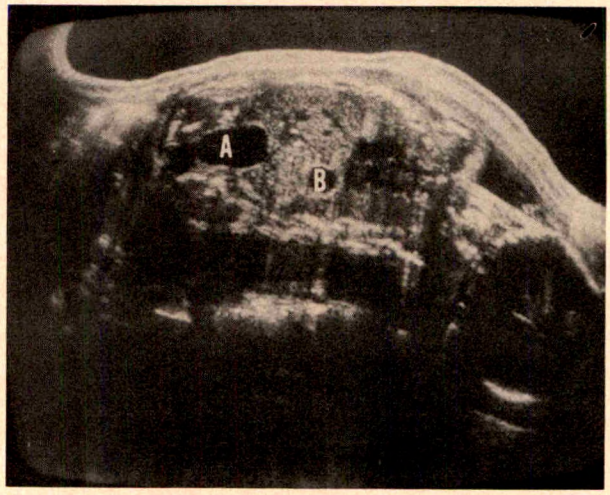


Fig. 9. Sagittal scan of normal fetal bladder *(A)* and stomach *(B)*.

aqueductal stenosis has been diagnosed in a previous male offspring, a fetal karyotype should be obtained. Although the index of suspicion is much greater in a male fetus, thorough sonographic evaluation of the fetal cranium should be performed in all fetuses unless there is clear genetic evidence for the X-linked variety.

A patient who was delivered of two male infants with hydrocephalus, the last of whom was diagnosed as having aqueductal stenosis, had an amniocentesis at 16 weeks which revealed a male fetus. Scans at 20 weeks suggested dilated lateral ventricles, and repeat examination at 23 weeks confirmed this impression. The BPD was within normal limits. Hydrocephalus with marked cortical thinning was found in the abortus.

In the third trimester the diagnosis of hydrocephalus is not difficult to make since the head circumference is often very large. In these cases, information obtained from ultrasound may be extremely useful in the patient's obstetric management. Because of improvements in shunting techniques, neurosurgeons can now offer a life of reasonable quality to some infants with hydrocephalus. Therefore, it is important that obstetricians confronted with a diagnosis of fetal hydrocephalus develop criteria which will aid them in choosing the route of delivery. With ultrasound it is possible to obtain BPD and head circumference measurements, to detect intracranial asymmetry with attendant deviation of the falx (the ultrasonic midline), and to measure the thickness of the cortex. There is extremely poor infant survival when the fetal head circumference measurement exceeds 50 cm. Also, a shift of the midline is usually associated with porencephalia which has an ominous prognosis. If the thickness of the cerebral cortex is less than 1 cm, this correlates with poor neurological potential. The ultrasonic diagnosis of hydranencephaly (absence of the cerebral cortex) has been reported.[20] This condition is not associated with infant survival; therefore, the prenatal diagnosis of this condition would be extremely valuable in the obstetric management of the patient. Since spinal defects are also noted in some cases of hydrocephalus and because large defects have a guarded prognosis, a careful spinal scan should also be performed. Vaginal delivery with decompression of the fetal head by aspiration is relegated only to those cases where the prognosis is hopeless. However, if there is a chance of survival with reasonable function based on the above information, then cesarean section should be performed once there is evidence of pulmonary maturity in the fetus.

During the study period, hydrocephalus was accurately diagnosed in five third-trimester patients. Cesarean section was performed in all five patients, including a woman who declined vaginal delivery despite significant porencephalia in the fetus, which was later confirmed in the infant by computerized tomography.

One misdiagnosis of hydrocephalus was made in an additional patient. She was referred from another hospital where the diagnosis of fetal hydrocephalus had been made ultrasonically. The fetal head was larger than average (BPD of 9.6 cm at 35 weeks compared with a mean and standard deviation of 8.6 ± 0.4 cm); the lateral ventricles seemed dilated, and there appeared to be a shift of the midline structures. Based on these findings, the infant was delivered by cesarean section at 37 weeks. Although the infant's head circumference was in the ninety-eighth percentile, he appeared to be neurologically normal. Computerized tomography was not performed until 9 weeks of age, at

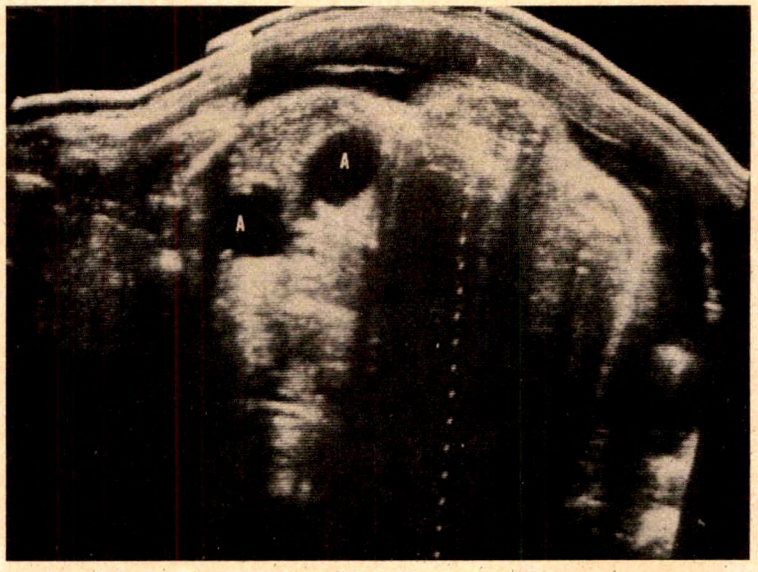


Fig. 10. Duodenal atresia. This 32 week fetus had a classic "double bubble" sign composed of dilated stomach and duodenum seen in duodenal atresia. *A:* Echo-spared areas.

which time there was no evidence of hydrocephalus.

There are structures in the fetal head such as the sylvian fissure which may be mistaken for the outer margin of the lateral ventricle. The distinction between structures, however, should be appreciated by scanning through the fetal head in many planes. Although many more patients will require ultrasonic evaluation before one can appreciate the true rate of false negative and positive diagnoses of hydrocephalus, it is hoped that the incidence of misdiagnoses will be negligible in the hands of a cautious and experienced ultrasonographer.

Neural tube defects.

ANENCEPHALY. In most cases anencephaly is not difficult to diagnose. With instruments of good resolution, it is possible to discern a poorly formed cranium by the fifteenth week of gestation. In later gestation, however, the cranial pole is often driven deep into the pelvis where it is difficult to evaluate ultrasonically. Even in normal pregnancy, an engaged cranium is occasionally too deep in the pelvis for ultrasonic visualization and anencephaly is erroneously suspected. In these cases pelvic examination and x-ray studies should be used for further evaluation.

During the study period, 82 patients at risk for neural tube defects, of whom 37 had previously been delivered of anencephalic fetuses, were examined in the second trimester. Well-formed craniums were found in all of these cases. In two other second-trimester patients who were not at risk, anencephaly was diagnosed at 15 weeks (Fig. 5) and 22 weeks when scans were performed to establish gestational age. The condition was also diagnosed in seven third-trimester patients referred because of clinically apparent hydramnios.

Spine. The efficacy of screening with maternal serum alpha-fetoprotein (AFP) determinations for neural tube defects is no longer questioned. Screening programs generate 2% to 3% of pregnancies which require further evaluation by ultrasound and amniocentesis.[34] In contrast to anencephaly, spina bifida is difficult to diagnose with ultrasound and requires significant operator experience. With large defects, splaying of the fetal spine can be noted in sagittal scans. However, if a defect is not seen on sagittal examination the diagnosis cannot be excluded until a series of carefully spaced transverse scans fails to identify an incompletely closed spinal segment.[3, 5, 17] Even with a detailed examination, the sacral spine often cannot be completely evaluated because of poorly defined landmarks in that area.

In 81 of 82 patients at risk for a neural tube defect the diagnosis of spina bifida was excluded with ultrasound and thus far normal babies have been born. Amniotic fluid AFP levels were also normal in these pregnancies. The other patient at risk, who had previously been delivered of an infant with anencephaly, was studied because the amniotic fluid AFP was 9 standard deviations above the mean for 16 weeks' gestation. Ultrasound evaluation revealed a small spinal defect in the upper lumbar area (Fig. 6). The defect was delineated with fetoscopy just prior to termination and at abortion an open spinal defect involving the eleventh thoracic vertebra through the second lumbar vertebra was found. It is of interest that the fetus actively moved

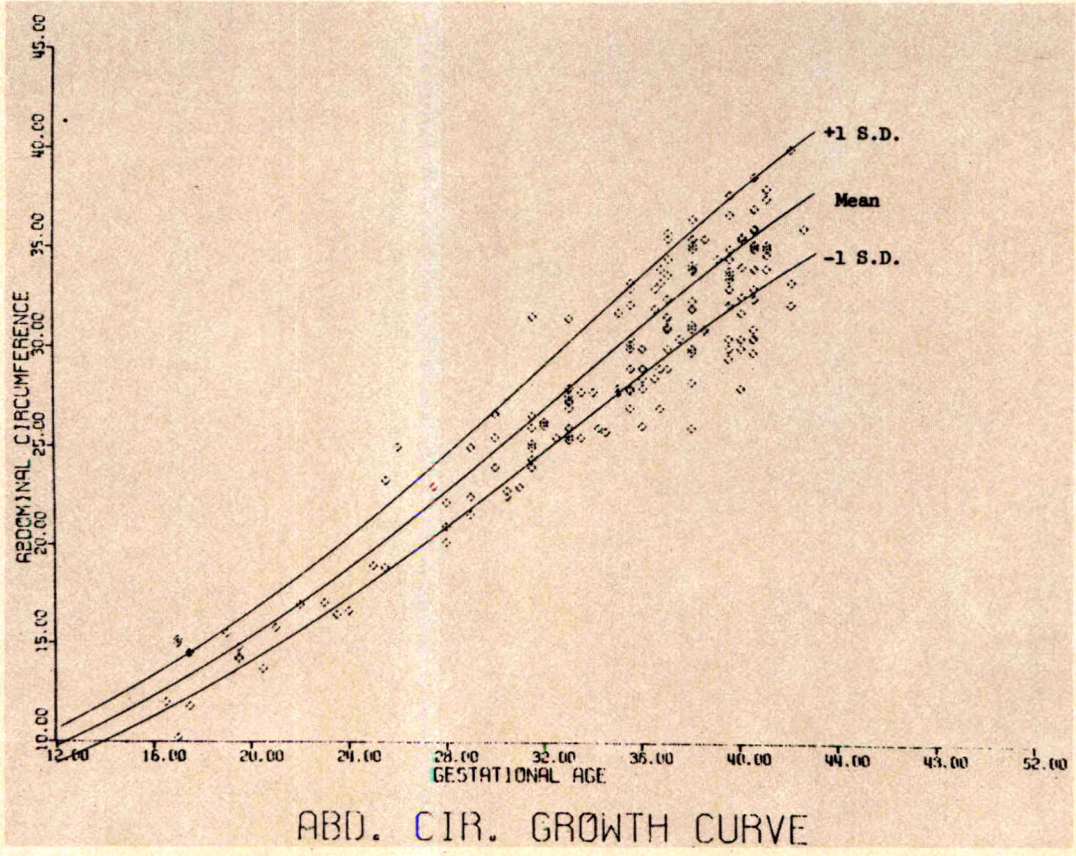


Fig. 11. Graph of abdominal circumference at different gestational ages. (From data generated by Warsof during preparation of reference 35.)

Table III. Mean fetal KC/AC ratios and standard deviations

	Gestational age (wk.)					
	≥16 (n =9)	*17-20 (n = 18)*	*21-25 (n = 7)*	*26-30 (n = 11)*	*31-35 (n = 19)*	*36-40 (n = 25)*
Mean	0.28	0.30	0.30	0.29	0.28	0.27
SD	±0.02	±0.03	±0.02	±0.02	±0.03	±0.04

Adapted from Grannum, P., Bracken, M., Silverman, R., and Hobbins, J. C.[15]

both legs during real-time examination, yet this defect most likely would have resulted in paralysis of the lower extremities after birth. Another investigator[4] has recorded active fetal leg movement in a fetus with a neurologically significant spinal defect. This phenomenon is difficult to explain.

Meningoceles, encephaloceles, and myeloceles present ultrasonically as saccular protrusions from the fetal cranium and/or spine.[16, 30] In the presence of oligohydramnios these conditions can be difficult to identify.

Chest. Investigators are beginning to evaluate fetal heart function with echocardiography.[17] We have been able to identify all four valves, observe the interventricular septum, measure chamber size, and calculate various echocardiographic indices.[19] Recently it has been possible retrospectively to diagnose tricuspid atresia and a hypoplastic right ventricle with echocardiographic studies.[19] There is little doubt that soon it will be possible consistently to measure systolic time intervals and also to identify some cardiac anomalies in utero such as hypoplastic ventricles, atretic valves, and ventricular septal defects.

Certain surgically correctable intrathoracic defects can be identified in late pregnancy with ultrasound. For instance, a large diaphragmatic hernia will present

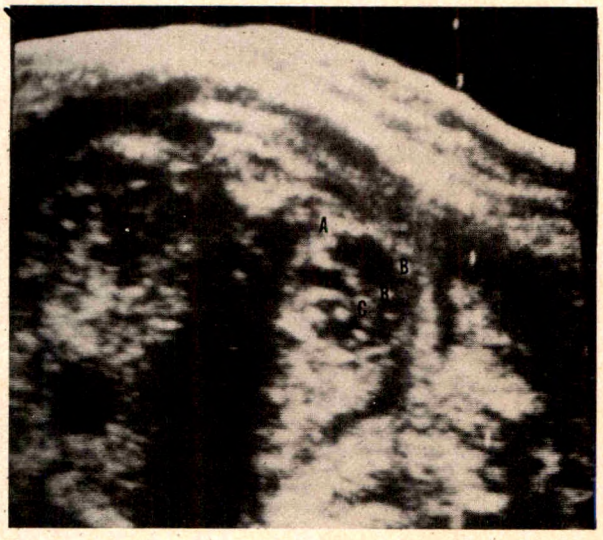


Fig. 12. Normal fetal kidneys. Internal structure is well demonstrated. *A:* Cortex; *B:* arcuate arteries; *C:* columns.

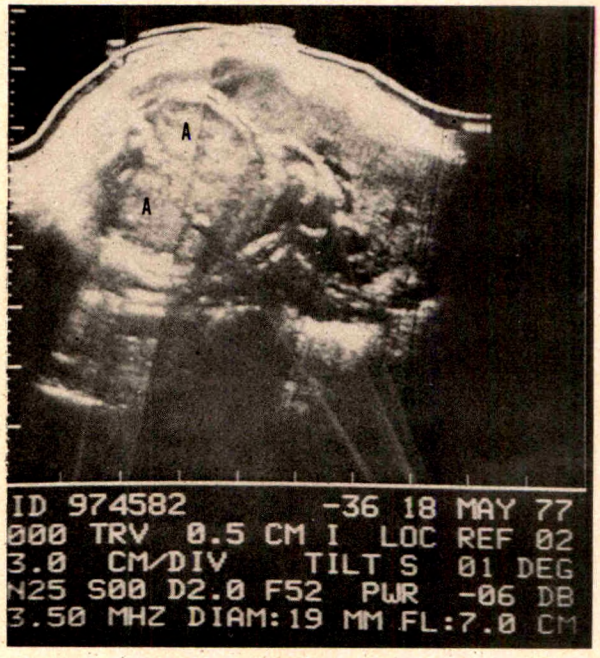


Fig. 13. Enlarged kidneys in 28 week fetus who had classic infantile polycystic kidneys *(A)* at birth.

as an echo-spared area within the chest next to the heart (Fig. 7). A transverse scan (Fig. 8) at the level of the diaphragm can reveal the defect. Since the mortality rate is high if this condition is unsuspected, prenatal diagnosis can be lifesaving to an affected infant because surgical correction of the defect can be instituted immediately after birth. We have diagnosed diaphragmatic hernia in a diabetic patient referred for evaluation of clinical polyhydramnios.[33] In another patient a posterior thoracic cyst was identified in a fetus prior to intrauterine death. At postmortem examination the cyst was of enteric origin.

The configuration and capacity of the chest can be evaluated with ultrasound. Real-time ultrasound offers the viewer a dynamic two-dimensional picture of fetal chest movement, a parameter which may have prognostic significance in high-risk pregnancies.[23] Real-time examination of the chest wall may also be useful in anomalous conditions resulting in pulmonary hypoplasia. We have examined nine second-trimester patients who previously had been delivered of infants with abnormal thoracic findings. Three fetuses were at 25% risk for either thoracochondrodystrophy (Charcot-Levin syndrome) (one case), or asphyxiant thoracic dysplasia (two cases). The other six patients had been delivered of fetuses with pulmonary hypoplasia. In each case the thoracic configuration was normal and the diameters appropriate for gestational age. Each woman gave birth to a normal infant.

In a patient referred because of polyhydramnios in the third trimester, the chest was found to be small in circumference when compared with the abdomen. During real-time evaluation, the fetus appeared to be making thoracic movements, but the excursions were of very small amplitude. Significant limb reduction was also noted. An infant with thanatophoric dysplasia (dwarfism) was born near term and died within a few hours following birth of respiratory distress.

Abdomen. The measurement of abdominal circumference at the level of the umbilical vein is an invaluable indicator of fetal mass,[6, 35] and the configuration of the abdomen may be an important clue to intra-abdominal pathology. In the presence of a normal volume of amniotic fluid it is generally easy to identify the umbilical cord insertion, therefore enabling the diagnosis of omphalocele and gastroschisis.[24] In patients with high serum or amniotic fluid AFP levels, the cord insertion site requires ultrasonic scrutiny since an omphalocele is often associated with elevated AFP.

Gastrointestinal tract. Ultrasonic findings in fetal gastrointestinal obstruction will depend upon the site of obstruction.[9] Under normal circumstances the fetal stomach appears as a circular echo-spared area in the left upper quadrant of the abdomen (Fig. 9). The intestines are represented by scattered echoes.

Theoretically, in esophageal atresia the stomach may or may not be visible, depending upon whether there is a communication between the trachea and esophagus distal to the obstruction. Also it is feasible that the stomach can secrete enough fluid in the presence of esophageal atresia to distend itself to ultrasonically definable proportions. However, since ultrasound

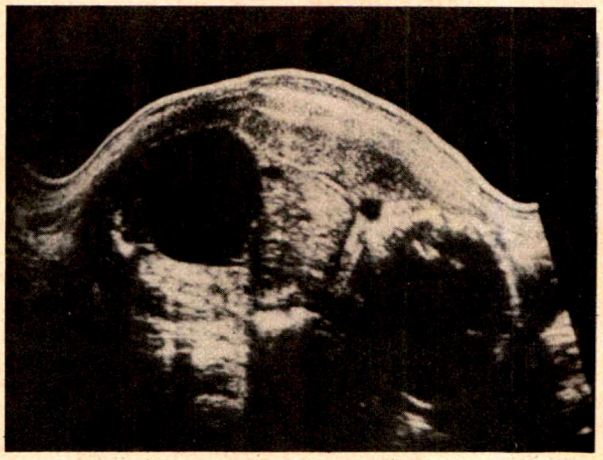


Fig. 14. Large cystic dysplastic kidney.

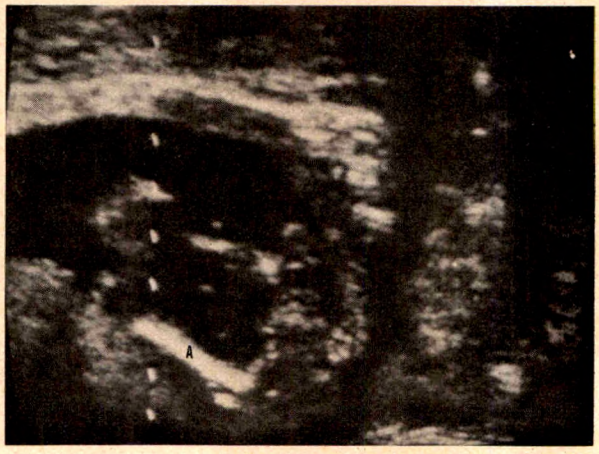


Fig. 15. Left femur *(A)* in normal 18 week fetus.

diagnosis of this condition has yet to be reported, the potential to diagnose esophageal atresia remains in question.

Duodenal atresia results in a markedly distending stomach and duodenum.[21] We have diagnosed this anomaly twice during the study period. In one patient a classic double area of echo sparing was noted (Fig. 10) and in the other a markedly dilated stomach was appreciated.

If multiple distended loops of bowel are noted, the diagnosis of ileus should be considered. One such infant was recently referred to our institution. The in utero ultrasound examination was compatible with the diagnosis of meconium ileus and the subsequent diagnosis of cystic fibrosis. Similar ultrasonic findings have been reported in association with anal atresia.[1]

We have noted dilated loops of bowel in an occasional patient in whom repeat scans did not confirm the original impression. It is suspected that in normal

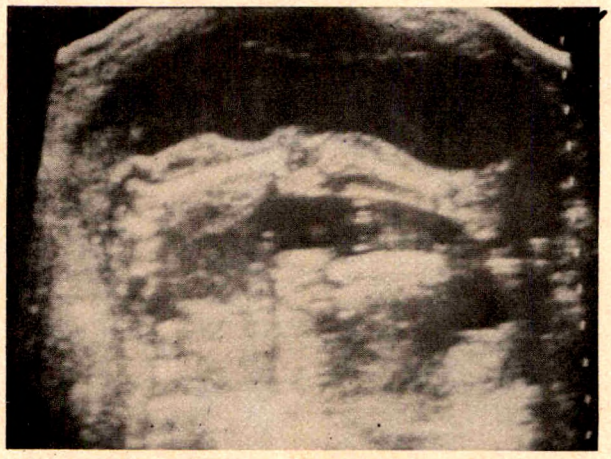


Fig. 16. Entire leg in 32 week fetus.

pregnancies transient dilation of the fetal bowel may be a normal phenomenon. Therefore, diagnosis of gastrointestinal pathology requires demonstration of ultrasonic findings on repeated scans made at least one week apart.

When dealing with an anomaly affecting gross body configuration, it is useful to compare the abdominal circumference with that of the thorax and head. A nomogram (Fig. 11) is presented from data generated in a previous study[35] in which abdominal circumferences were measured at different times in gestation. By using these measurements for reference, the visual impression of abdominal protuberance can be confirmed quantitatively.

Urinary tract. Fetal kidney size and composition can be determined with high-resolution ultrasound equipment (Fig. 12). On a transverse scan at the umbilicus the kidneys will appear as two circular structures on either side of the spine. The size of these kidneys, relative to the size of the fetal abdomen, can be quantitated (Table III). A recently constructed nomogram[15] comparing abdominal circumference with the mean kidney circumference (KC/AC ratio) is presented for reference.

The fetal bladder is frequently identified at 18 weeks and should be visualized in almost all cases after the twentieth week of gestation. Identification of the bladder precludes the diagnosis of nonfunctioning polycystic kidneys or renal agenesis. Failure to visualize the bladder could simply mean the fetus has recently voided. However, if the bladder is not identified by an experienced ultrasonographer after the twentieth week of gestation during scanning sessions spaced over a period of an hour and a half, inadequate renal function should be strongly considered.

We have examined two patients who had previously

Table IV. Postmortem external measurements (in centimeters) in control fetuses and ultrasound measurements in Cases 1 and 2

Measurement	*Controls**	*Case 1*	*Case 2*
Biparietal diameter	3.8 ± 0.3	4.0	3.7
Forearm length	3.0 ± 0.2	3.3	–
Arm length†	8.2 ± 0.5	8.6	–
Humerus length	3.7 ± 0.3	–	2.5 (P<<0.001)
Femur length	3.7 ± 0.2	–	2.8 (P<<0.001)

From Mahoney, M. J., and Hobbins, J. C.: Prenatal diagnosis of chondroectodermal dysplasia (Ellis-van Creveld syndrome) with fetoscopy and ultrasound, N. Engl. J. Med. **297:**258, 1977, published by the Massachusetts Medical Society.

*Mean ± SD from 22 fetuses of gestational (menstrual) ages of 16 to 20 weeks.

†Measured from shoulder to end of third finger.

been delivered of infants with Potter's syndrome due to renal agenesis. There was a 5% risk of recurrence. Normal-sized kidneys and bladder were demonstrated in each fetus at 18 and 20 weeks' gestation, respectively.

Another cause of Potter's phenotype in a stillborn or newborn infant is infantile polycystic kidney disease, an autosomal recessive disorder with a 25% recurrence rate. If the kidney disease process is advanced at birth, the kidneys are large and show innumerable small cysts on the cut surface. These cysts measure about 1 mm in diameter and represent cystic dilatation of the tubules. The expected ultrasound findings are enlarged, solid-appearing kidneys rather than kidneys with many echo-spared areas typical of larger cysts. Some infants with this disease show prolonged survival. In these instances, the kidneys might not show the enlargement typical of the more severe cases.

We have studied with ultrasound four pregnancies in two patients at risk for infantile polycystic kidney disease. One patient was referred at 28 weeks for sonography. Oligohydramnios and markedly enlarged, solid-appearing kidneys (Fig. 13) were noted. KC/AC ratio was 0.48 (control mean, 0.29 ± 0.02 SD). A stillborn infant was delivered at term with nonfunctioning polycystic kidneys (by histology) and pulmonary hypoplasia. Sonography was performed at 18 and 22 weeks of gestation in the patient's following pregnancy. The KC/AC ratios were 0.28 and 0.29. The TIUV was within 1 SD of the mean for gestation and a bladder was seen. The diagnosis of nonfunctioning kidneys was excluded and the pregnancy continued. At term the infant encountered no problems and an intravenous pyelogram appeared normal.

Another patient was delivered of two stillborn infants with the autopsy diagnosis of infantile polycystic disease. Ultrasound evaluation in the twenty-eighth week of gestation revealed bilaterally enlarged solid kidneys (KC/AC ratio = 0.44). The 36 week infant was stillborn with classic Potter's phenotype and kidney pathology. The patient's last pregnancy was interrupted at 24 weeks. The KC/AC ratio at 20 weeks was 0.40 (four standard deviations above the mean). The bladder was not seen; marked oligohydramnios was present, and TIUV measurements were more than three standard deviations below the mean for gestation. Amniotic fluid protein concentration was elevated

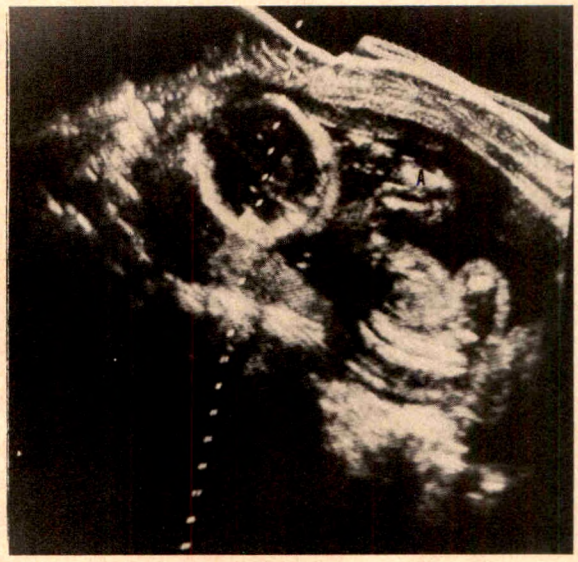


Fig. 17. Short-limbed dysplasia. Entire right arm is visualized *(A)*. Measurement is significantly shorter than mean for gestation.

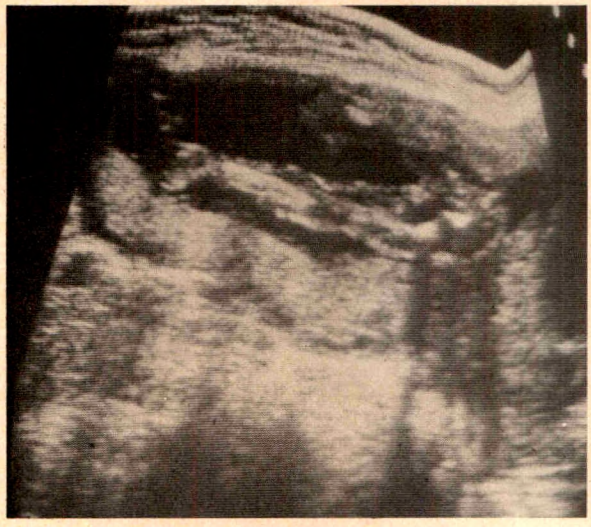


Fig. 18. Normal lower limbs in patient at risk for short-limbed dysplasia.

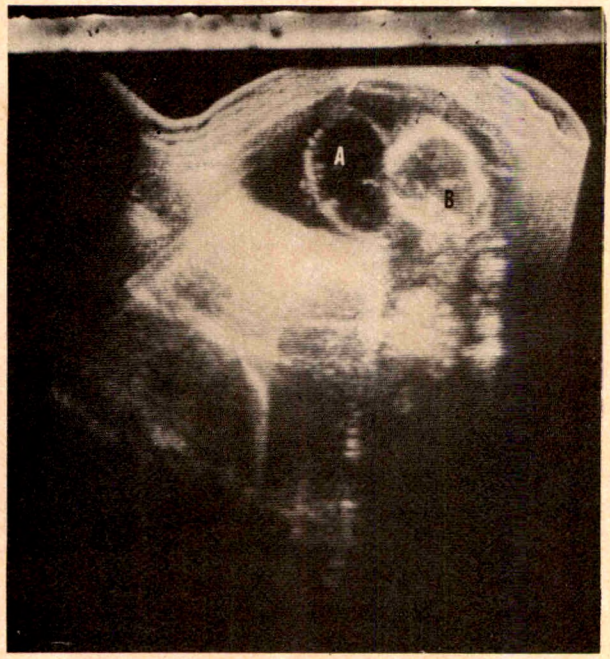


Fig. 19. Sac *(A)* behind fetal head *(B)* in 20 week fetus with lymphangiectasia.

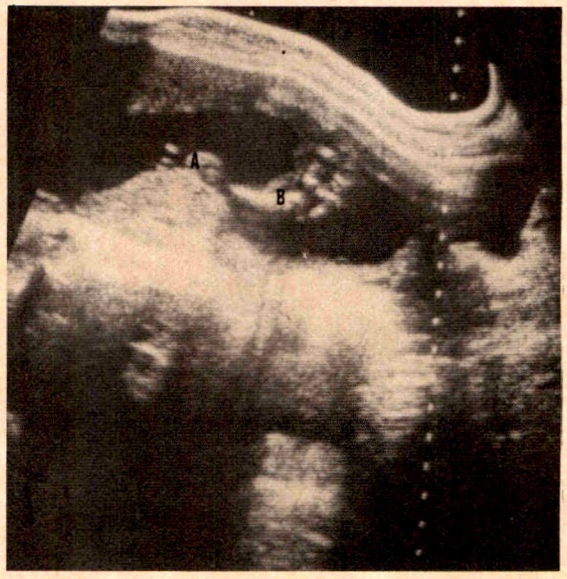


Fig. 20. Roberts syndrome. Diagram of hand fragments *(A)* and humerus *(B)*.

to 4.1 g/dl (four to eight times normal). At autopsy, amnion nodosum, Potter's facies, and a contracted bladder were noted. The kidneys were slightly larger than normal but did not show the classic histologic dilation of tubules which is associated with the disease. A cause other than polycystic kidney disease may have led to oligohydramnios in the second trimester (a rare finding). Alternatively, it is possible that dilatation of the tubules had not yet progressed to a stage of histologically recognizable disease although renal function was severely impaired.

Fetal kidney pathology can also occur in patients without a history of fetal anomalies. In a patient scanned at 23 weeks to determine gestational age, enlarged kidneys were noted (KC/AC ratio of 0.45). Multiple large cysts measuring 5 to 15 mm were present within the kidneys and marked oligohydramnios was noted. A stillborn infant was born at 37 weeks with multicystic kidney disease.

Obstruction of the urinary tract will produce ultrasound findings which vary according to the level of obstruction.[27] Urethral strictures, for example, will result in a massively enlarged bladder and hydronephrotic kidneys. In one case in the study urethral stricture was also associated with bilateral dysplastic kidneys, one of which contained a single 10 cm cyst (Fig. 14). It is conceivable that by continuously draining the fetal bladder in cases of posterior urethral valve anomalies the kidneys could be protected from significant hydronephrosis.

Extremities. There are a variety of congenital and acquired conditions which affect the fetal limbs. These include certain forms of short-limbed dysplasia such as Ellis-van Creveld syndrome (chondroectodermal dysplasia) associated with a 25% recurrence rate, thanatophoric dysplasia recurring in 2% of cases, and phocomelia syndromes.

Recent attention has been drawn to the association between ingestion of progestogens in the first trimester of pregnancy and limb reduction defects,[18] although prospective data are lacking.[7] Abnormal limb anatomy may accompany congenital syndromes involving other organ systems. For instance, 12% of infants with Fanconi's anemia (with a 25% recurrence rate) have an absent or hypoplastic radius. This finding in a fetus at risk would strongly suggest the fetus was affected.

It is distinctly feasible to measure limb length and individual bone length in the fetus at risk. Measurement of limb length requires significant operator experience, because tangential sections through the limb will produce measurements that are spuriously short. Real-time ultrasound is useful to quickly delineate the proper plane in which to scan with compound contact equipment. The most accessible bone in the very active second-trimester fetus is the femur (Fig. 15). The humerus also can be outlined, but with more difficulty. Since in most cases the fetal limbs are flexed, measurement of an entire limb is possible only if the fetus is

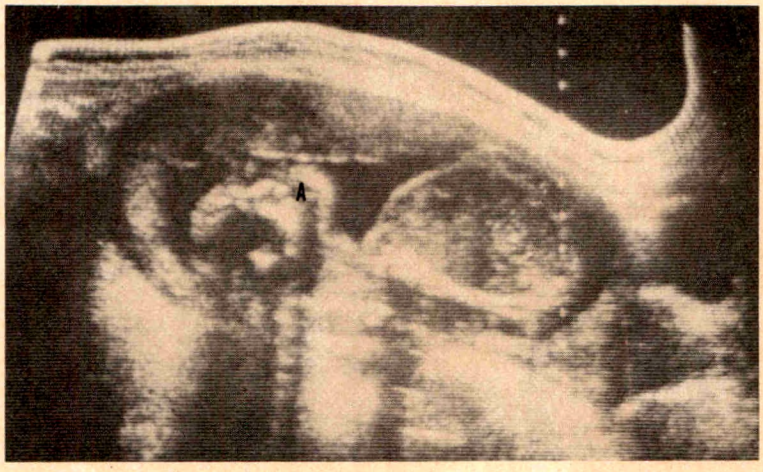


Fig. 21. Roberts syndrome. Premaxillary protuberance *(A)*.

caught by chance with a limb extended (Fig. 16) or when a drug, such as diazepam, is used to diminish fetal movement.

We have obtained control measurements of several limb and individual bone lengths from autopsy data (Table IV). In two of three cases at risk for Ellis-van Creveld syndrome,[22] femoral and humeral lengths were within one standard deviation of the mean. These fetuses were normal at birth. In the other patient the right humerus length and left shoulder-to-hand length were four standard deviations below the mean for gestation. The diagnosis of Ellis-van Creveld syndrome was confirmed on the abortus. In another patient (Fig. 17) who had previously been delivered of a fetus with a poorly defined type of skeletal dysplasia, fetal femur length and arm length were more than four standard deviations below the mean at 23 weeks' gestation. An infant with compomelic dysplasia was born at term. Five other patients were examined who were carriers of other forms of short-limbed dysplasia. Normal limb measurements were obtained (Fig. 18) and the infants were normal at birth. A fetus at risk for Fanconi's anemia was scanned and arm anatomy was found to be normal. This was also confirmed at birth.

Multisystem anomalies. A variety of unclassified multiple anomaly patterns can be diagnosed by ultrasound in the second and third trimesters. Often ascites is a consistent feature. In some cases a scan will demonstrate obvious definable abnormalities, but a definitive diagnosis cannot be made because of similarities to other disease entities. For example, we identified a sac behind the fetal head (Fig. 19) in one second-trimester patient. This finding was compatible with meningocele. However, the stillborn fetus was born with a rare condition, lymphangiectasia, in which the integument is dissected away from the underlying fascia by lymphatic accumulation.

We have also examined four pregnancies at risk for Roberts syndrome, a condition with multiple anomalies including tetraphocomelia, cleft lip and palate, genital hypertrophy, and nonfunctioning kidneys. There is a 25% chance of recurrence. One patient was studied in two successive pregnancies. She had previously been delivered of a stillborn infant with Roberts syndrome. In the next pregnancy she was referred for ultrasound evaluation at 20 weeks. The TIUV was more than four standard deviations below the mean for gestation, marked oligohydramnios was noted, and premaxillary swelling and a protuberant abdomen were noted. The bladder was not visualized and the extremities could not be well evaluated because of the oligohydramnios. Abortion was induced and the fetus was found to have Roberts syndrome with nonfunctioning dysplastic kidneys. In the next pregnancy the TIUV was within normal limits and normal-sized kidneys and bladder were demonstrated. However, markedly shortened femurs were noted along with a virtual absence of the radius and ulna bilaterally (Fig. 20). A protuberant maxilla was also delineated ultrasonically (Fig. 21). All of the above findings were found in the aborted fetus.

Osteogenesis imperfecta congenita is an inherited disease in which pathologic fractures of the long bones, ribs, and cranium are seen in infants born with the condition. Although it was postulated that these fractures could be present in the second trimester, confirmation of this hypothesis was only recently established.[32] They were able to diagnose two cases in 16

fetuses at risk by ultrasound identification of fetal fractures at 19 weeks in conjunction with elevated amniotic fluid pyrophosphate levels.

Comment

The experience with fetal ultrasonography reported here demonstrates the wide range of fetal morphology and function that can now be assessed. By outlining surface anatomy and identifying internal organ anatomy in the fetus, it is possible for the ultrasonographer to diagnose anomalies of the cranium, spine, gastrointestinal tract, urinary tract, and extremities. The predictive capacity of ultrasound is often enhanced when other diagnostic tests such as x-ray examination or serum and amniotic fluid fetospecific protein analysis are used.

This diagnostic capability is greatly enhanced by complete and accurate family and genetic history taking, including detailed information about previous stillborn or aborted fetuses. Many congenital anomalies have recognized modes of inheritance or empiric data for recurrence risks, and information from patient history will identify women who are candidates for early ultrasound examination. Patients exposed to potential teratogens whose effects are known may also benefit from sonographic diagnosis. Furthermore, a discrepancy between uterine size and dates should alert the physician to conditions which have the potential of diagnosis with ultrasound examination.

It must be stressed here that many of the diagnoses described in this review require significant operator experience and that some unusual ultrasonic findings are not necessarily associated with fetal pathology. Fluid-filled loops of bowel can mimic a distended urinary tract, and the fetal abdomen can contain other echo-spared areas which are unassociated with intra-abdominal abnormalities. Every effort must be made to define normal variations in fetal morphology and rule out sources of artifact.

In the future ultrasound technology will progress to a point where three-dimensional imagery will become a reality. With this enhanced capability to delineate entire organs and to measure volumes, it will then be possible more precisely to diagnose specific fetal anomalies.

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COMMUNICATIONS IN BRIEF

This section is suitable for reporting results of therapeutic trials, descriptions of new procedures or instruments, and case reports which illustrate a principle. Reports should be limited to seven hundred words and two references. Use of an illustration or table requires a proportionate reduction in total words.

An unusual case of ovarian tumor

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SEVERAL ovarian tumors have been associated with calcification, with or without systemic hypercalcemia: gonadoblastoma, teratoma/dermoid, dysgerminoma.[1] The calcification in these tumors had irregular, confluent, or rounded pattern. In mature cystic teratoma we frequently have bone well formed, but this fact occurred in a focal area.[2] We report a case in which an ovarian osseous cyst was diagnosed at the pathologic examination.

A 42-year-old woman was admitted to the hospital with a pelvic calcified mass. She complained of abdominal pain, especially during sexual intercourse.

An operation was performed and a right ovarian tumor, rounded, with no adhesiveness to neighboring structures, was excised. Pathologic examination of the specimen demonstrated a nodular tumor, 6.0 by 6.0 by 5.0 cm. In cut-surface view this tumor was a cyst with osseous wall and yellow and limpid fluid (Fig. 1). A roentgenographic view demonstrated a consistent osseous matrix in the walls of the cyst (Fig. 2). Routine histologic examination, after decalcification, revealed compact and trabecular mature osseous tissue in lamellar pattern (Fig. 3). Focal hematopoietic marrow tissue within osseous trabeculas was observed. No epithelial cells were identified in the tumor.

The patient was well postoperatively.

In the case reported here we have an unusual ovarian cystic tumor. No similar cases could be found in the literature and we have no histologic elements to determine the pathogenesis of this tumor.

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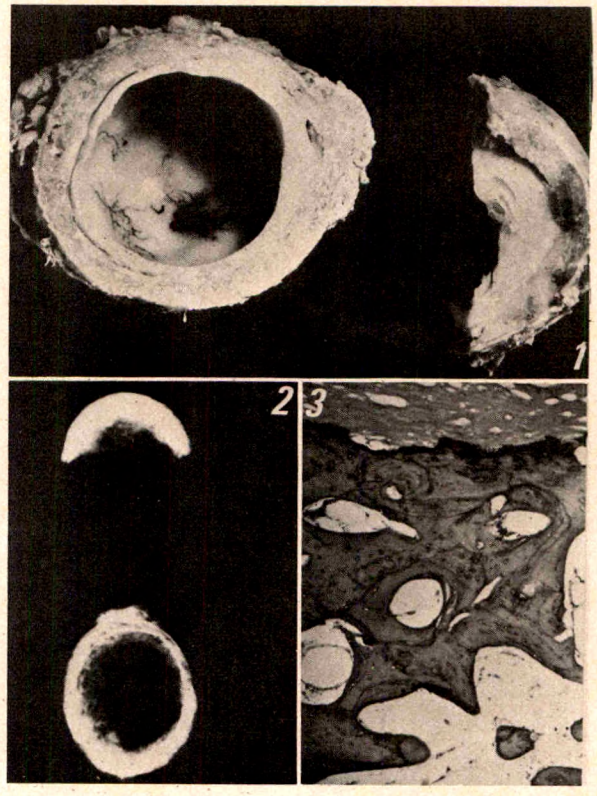


Fig. 1. A macroscopic cut-surface view of the tumor with a large osseous wall. The vascularization in the internal surface is evident.
Fig. 2. Roentgenographic view of the specimen; dense osseous matrix in the walls.
Fig. 3. Histologic section demonstrating a mature lamellar bone in the wall of the tumor.

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Fetal tachycardia prior to the development of hydrops—Attempted pharmacologic cardioversion: Case report

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ALTHOUGH FETAL tachyarrhythmia is now a recognized cause of hydrops, previous case reports have not documented the appearance of the tachycardia prior to the development of hydrops. We report a case of fetal supraventricular tachycardia in which prenatal administration of digoxin and propranolol to the mother failed to convert the arrhythmia or prevent the development of hydrops.

A 30-year-old white woman, gravida 3, para 2, presented at $28^{1}/_{7}$ weeks' gestation complaining of abdominal cramping of 12 hours' duration. Both the physical examination and sonographic examination revealed an active fetus with a heart rate of greater than 240 bpm.

The diagnosis of fetal tachyarrhythmia was made, and the mother was given an intravenous loading dose of digoxin 1.25 mg, followed by maintenance digoxin 0.25 mg by mouth four times a day. Propranolol at a dose of 20 mg, by mouth four times a day, was started 8 hours after the digoxin. Two days later the propranolol dose was increased to 40 mg by mouth four times a day.

After 4½ days with no change in the fetal heart rate, and the mother having physical signs of digoxin toxicity, the digoxin was discontinued and the propranolol tapered. Her fundal height rapidly increased over the next 2 days and polyhydramnios was suspected. Fetal ascites was present on sonographic examination. Because of the immaturity of the fetus, it was decided to continue observation without any active intervention.

At $31^{3}/_{7}$ weeks' gestation, 23 days after the fetal tachycardia was first discovered, the mother was delivered of a 2,250 gram hydropic male infant.

The infant had Apgar scores of 3 and 6 and required tracheal intubation and mechanical ventilation. At birth, the heart rate was 120 bpm but increased to more than 200 bpm on admission to the nursery. Physical examination revealed a hydropic male infant with a single umbilical artery but no other anomalies. The infant was not clearly in congestive heart failure.

Attempts to convert the arrhythmia with digoxin and edrophonium chloride (Tensilon, Roche Laboratories) were unsuccessful. Despite our initial inability to successfully convert the tachyarrhythmia, the infant slowly improved. By the fourth day of life, the infant's weight had decreased to 1,700 grams (the fiftieth percentile for a 31 to 32 week infant). The tachyarrhythmia persisted until oral propranolol was administered, with rapid successful pharmacologic cardioversion. The electrocardiogram was consistent with a Wolf-Parkinson-White type A pattern. At 39 days of life, the infant was discharged with a normal sinus rhythm and in apparent good health.

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More than 50 cases of probable fetal tachyarrhythmia have now been reported. Levkoff,[1] from a review of 17 cases, concluded that the tachyarrhythmia is benign and should not be a cause for delivery.

A review of recent case reports, however, does not support the observation that fetal tachyarrhythmia is always benign. A fetal death has been noted in association with a heart rate of 350 bpm.[2] Morbidity has included hydrops and lesser degrees of fetal-maternal water imbalance, early-onset heart failure, hypoglycemia, and prematurity. While no neonatal deaths have been reported, mechanical ventilation and direct current cardioversion have occasionally been necessary for the management of these infants. Digitalis toxicity in the infants has been frequently reported.

Because of the potential fetal and neonatal complications, we attempted to pharmacologically convert the arrhythmia in utero. Digoxin is known to cross the placenta, but there is no information concerning the length of time needed to achieve therapeutic digoxin concentrations in the fetus. The arrhythmia in our patient did not respond to established therapeutic concentrations of digoxin in the neonatal period; thus it is not surprising that we could not convert the arrhythmia in utero.

Propranolol, a β blocker used for the treatment of paroxysmal supraventricular tachycardia, is also known to cross the human placenta. Since propranolol has been reported to adversely affect the fetus at birth, our intent was to withdraw this drug prior to the onset of labor. Why our patient responded quite rapidly to propranolol in the neonatal period but not in utero is unclear. With the known large variation in plasma concentrations following oral administration, it is quite possible that therapeutic concentrations were not achieved in the mother. As with digoxin, there is inadequate knowledge concerning the length of time necessary to achieve a therapeutic fetal tissue concentration.

The fetus in the present case report developed sonographic evidence of ascites within 1 week of admission. At 28 weeks, the risk of neonatal death led us to feel that termination of the pregnancy would be unwise. Weekly sonographic examinations and careful collection of fetal activity data would appear to be a reasonable approach to management in those infants too immature to be delivered. Despite our negative results, we feel that in those cases where termination of

pregnancy is not justified, pharmacologic intervention should be attempted in order to avoid the complication of fetal hydrops.

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Uterine rupture with the use of vaginal prostaglandin E_2 suppositories

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THE USE OF prostaglandin E_2 (PGE_2) vaginal suppositories for the termination of pregnancy in the mid trimester, induction of labor in cases of death in utero up to 28 weeks' gestation, and termination of benign molar pregnancy have recently been approved by the Food and Drug Administration (FDA).

A case of spontaneous rupture of the uterus following induction of labor for mid-trimester termination of pregnancy by intravaginal PGE_2 suppositories is reported.

A 23-year-old woman, gravida 3, para 1, presented at 23 weeks' gestation to the prenatal clinic of The Mount Sinai Medical Center, New York.

Termination of pregnancy was recommended on the basis of severe chronic hypertension due to diabetic renal disease and advanced diabetes mellitus (Class F). Uncontrollable hypertension during her previous pregnancy had resulted in a premature delivery at 34 weeks by low-flap transverse cesarean section.

The patient was admitted for evaluation and stabilization; B-scan ultrasonography showed a fetal biparietal diameter of 5.5 cm, consistent with 23 weeks' gestation, and clinical evaluation of uterine size was confirmatory. The blood pressure at the time of admission was 240/120 mm Hg. Funduscopic examination revealed proliferative retinopathy. The remaining physical examination was noncontributory.

The hemoglobin was 9.9 gm/dl, the white blood count was 12,600 with a normal differential, the serum creatinine was 3.9 mg/dl, and electrolytes and coagulation profile were within normal limits. A 24 hour urine collection for protein was 3 gm.

The blood sugar was satisfactorily contolled on 36 units of NPH insulin and the blood pressure was reduced to satisfactory limits on diuretics (spironolactone 250 gm. three times daily and furosemide 40 mg daily).

On day 5 of hospitalization no fetal heart beat could be detected by Doptone or real-time ultrasonography. The fetal lie was transverse within the uterine cavity; the vertex pointed toward the left uterine wall. The height of the fundus was 2 cm beneath the umbilicus. A first vaginal suppository containing 20 mg of PGE_2* was inserted and within 90 minutes regular contractions were noted sufficiently severe to require sedation with 75 mg of meperidine. Despite continuous reinsertion of vaginal suppositories at 4 hourly intervals, a decrease in uterine activity was reported over the following 12 hours.

Clinical re-evaluation at this stage revealed a slight additional decrease in uterine height, with a bulging lower uterine segment and a cervix only 1 to 2 cm dilated with partial effacement. The membranes were thought to have ruptured because clear non–blood-stained fluid drained from the vagina. The patient was asymptomatic apart from mild intermittent lower abdominal pain. The abdomen was soft, with no signs of peritoneal irritation, and oxytocin augmentation at a rate of 16 mμ/min was instigated.

Over the ensuing 24 hours six additional PGE_2 suppositories were inserted, with no change in the cervical dilatation or effacement. At this stage a dilatation and extraction was attempted under general anesthesia. However, no products of conception were noted within the uterine cavity and a defect in the left lateral uterine wall was recognized. On exploratory laparotomy an intact sac containing all products of conception was found floating free within the upper abdomen. A transverse rupture of the lower uterine wall was noted†; no free blood was observed within the peritoneal cavity. A total abdominal hysterectomy was performed and the patient's postoperative course was marked by episodes of electrolyte inbalance. She was discharged on postoperative day 8.

No case of uterine rupture in conjunction with the use of vaginal PGE_2 suppositories has been reported.‡ The recent approval of this drug for the abortion of mid-trimester pregnancies and induction of labor in association with death in utero and benign molar disease by the FDA increases the actuality of the present report.

Prostaglandins increase intrauterine pressure to levels far beyond that of normal labor.[1] The increased risk of uterine rupture after previous cesarean section is well recognized.[2] This case raises questions about the presently unlimited use of vaginal PGE_2 suppositories with previously scarred uteri.

In retrospect it must be assumed that uterine rupture in this case occurred within the first 12 hours of labor, prior to oxytocin stimulation. A decrease in uterine size and cessation of labor represent fairly typical signs of uterine rupture.[2] Other classical signs, such as vaginal bleeding and peritoneal irritation as a conse-

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*Upjohn Company, Kalamazoo, Michigan.

†Photographic evidence is available on request.

‡Gutknecht, G. D., and Hendriks, J. W., The Upjohn Company, Kalamazoo, Michigan: Personal communication.

quence of intraperitoneal hemorrhage, severe pain, and unstable vital signs were lacking and resulted in a delay of diagnosis.

If PGE_2 suppositories are to be used in previously scarred uteri, utmost caution must be taken in order to recognize early signs of uterine rupture. The vaginal route of prostaglandin administration may carry the same risk for uterine rupture as has been reported for the intra-amniotic installation.

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Preinduction use of laminaria for the unripe cervix

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LAMINARIA TENTS have been shown to be safe and effective in causing cervical dilatation and in decreasing the duration of labor when used in the second and third trimesters.[1, 2] We wish to report the results of an ongoing investigation of laminaria as an adjunct to indicated induction of labor in a select population of patients with differing maternal or fetal factors demanding delivery in the face of an uninducible (low Bishop score) cervix.

The study group were inpatients on the maternal-fetal special-care unit who had been scheduled for induction prior to enrollment in the study by the attending physician because of maternal (pre-eclampsia, diabetes mellitus [Class B, C, or D]) or fetal (isoimmune hemolytic disease) indications. Fetal maturity had been verified by ultrasound and L/S ratio in all cases. Cervical dilatation of less than 1 cm and effacement of less than 50% was a precondition for inclusion in this study. Additionally, vertex presentation, intact membranes, and absence of bleeding or evidence of placenta previa were required. The study protocol had been approved by the human investigation review board.

After informed consent had been obtained, patients were randomly allocated to either the laminaria group or the control group. Patients in the laminaria group underwent intracervical placement of 6-10 size 6B laminaria tents (Mizutani Laminaria, Inc.) after Betadine preparation of the cervix at 1800 hours on the evening prior to planned induction. Retention of laminaria was encouraged by placement of a small Betadine-impregnated vaginal gauze pack. Control patients underwent the same procedure except for placement of laminaria. Sponges and laminaria were removed at 0600 to 0700 hours the next morning.

Table I. Bishop scores prior to and after treatment

	No.	*Bishop score before treatment (mean ± S.E.)*	*Bishop score after treatment (mean ± S.E.)*	*p*
Control patients	5	2.0 ± 0.4	2.4 ± 0.2	$p > 0.05$
Laminaria	7	2.3 ± 0.4	6.3 ± 0.9	$p < 0.005$

Bishop's score was determined by the same examiner (F. F.) in all patients immediately prior to laminaria or control placement and immediately following removal the next morning. The patients, the physician evaluating cervical response (F. F.), and the physicians managing subsequent induction of labor were all unaware of whether the laminaria or control procedure had been employed.

The use of laminaria effected a significant ($p < 0.005$) increase in Bishop score from 2.3 ± 0.4 to 6.3 ± 0.9 (Table I). Baseline Bishop scores were not different between the two groups ($p > 0.05$) nor did sham treatment result in a significant change in Bishop score ($p > 0.05$) (Table I).

Meaningful comparison of the course of labor between the control and laminaria groups is difficult as there were only seven vaginal deliveries among the 12 patients. All labors were initiated with intravenous oxytocin; amniotomies were generally reserved for the active phase of labor. Among the five control patients, there were only two vaginal deliveries after labors of 20 and 31 hours; cesarean sections were performed in three patients for failure to progress, prolapsed cord, or fetal distress. Five of the seven patients receiving laminaria were delivered vaginally after a mean duration of labor of 18 hours (range 12.5 to 29 hours). One cesarean section in the laminaria group was performed for failure to progress after secondary arrest in the active phase of labor (22 hours) and the other cesarean section was performed for fetal distress after 6 hours of labor.

Laminaria were responsible for a variable degree (usually mild) of crampy pelvic discomfort, and one patient who received laminaria was in early labor the morning after placement. Bleeding, amnionitis, and endometritis did not occur among patients receiving laminaria.

Laminaria tents are effective in increasing the apparent inducibility of the unripe cervix at or near term

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and appear safe and useful in selected patients. In this study, laminaria effected sufficient cervical change to permit amniotomy and direct fetal and intrauterine monitoring. Confirmation of a salutary effect on the course of subsequent induction and of acceptability morbidity awaits a larger experience with this technique. Continued carefully monitored investigation of the use of laminaria for indicated induction of labor is warranted.

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International Symposium: Adrenal Androgens

The International Symposium, "Adrenal Androgens" will be presented at the University of Siena, Siena Italy, October 8-9, 1979.

For information contact: Professor A. R. Genazzani, Cattedra di Patologia Ostetrica e Ginecologica, Via P. Mascagni, 46, 53010 Siena, Italy.

Gynecology: Up-to-Date Concepts in the Management of Common Problems

"Gynecology: Up-to-Date Concepts in the Management of Common Problems" will be presented August 27-30, 1979, at The Mark, Vail, Colorado.

For further information contact: The Office of Postgraduate Medical Education, University of Colorado School of Medicine, 4200 E. Ninth Ave., Denver, Colorado 80262. Telephone: (303) 394-5241.

Fourth International Congress on Gynecologic Endoscopy

The American Association of Gynecologic Laparoscopists will hold its Eighth Annual Meeting and present the Fourth International Congress on Gynecologic Endoscopy, November 4-9, 1979, at Caesars Palace, Las Vegas, Nevada.

For information contact: Jordan M. Phillips, M.D., 11239 South Lakewood Blvd., Downey, California 90241.

The Second Biennial Leadbetter Symposium: Sexual Dysfunction and Reproductive Biology

The Second Biennial Leadbetter Symposium: "Sexual Dysfunction and Reproductive Biology" will be presented September 6-8, 1979, at the University of Minnesota. The Symposium will include a systematic review of male and female infertility and male impotence including recent advances in relevant basic science.

For information contact: Leadbetter Symposium, c/o Continuing Medical Education, University of Minnesota, Box 293 Mayo Memorial Bldg. 420 Delaware St. SE, Minneapolis, Minnesota 55455.

Fifth International Meeting of the Groupe pour L'Advancement de la Microchirurgia

The Fifth International Meeting of the Groupe pour L'Advancement de al Microchirurgia will be held September 12-16, 1979, at Gardone on the Lake of Garda, Brescia, Italy. There will be a panel on "Neurosurgery" and one on "Gynecology."

For information contact: Prof. Giorgio Brunelli, 2A ORTOP, Spedali Civili, Brescia, Italy.

International Symposium on the Physiopathology of the Human Ovary

The International Symposium on the Physiopathology of the Human Ovary will be held in Rome, Italy, on September 14-18, 1980, at the Cavalieri Hilton Hotel.

Information may be obtained from: Dr. S. Iacobelli, Laboratorio di Endocrinologia Molecolare, Istituto di Clinica Ostetrica e Ginecologica, Università Cattolica, Via della Pineta Sacchetti 644, 00168 Roma, Italy. Telephone: (06) 3305-496. Telex: UNICATRO.

Second Annual Seminar in Current Aspects of Obstetrics and Gynecology

The Second Annual Seminar in Current Aspects of Obstetrics and Gynecology will be presented August 12-16, 1979, at Colby College, Waterville, Maine.

Inquiries should be directed to: Robert H. Kany, Director, Special Programs, Colby College, Waterville, Maine 04901.

Annual Clinical Meeting of Association of Planned Parenthood Physicians

The Annual Clinical Meeting of the Association of Planned Parenthood Physicians will be held in Philadelphia, Pennsylvania, at the Hilton Hotel, October 11-12, 1979.

For information contact: George R. Huggins, M.D., Secretary, Planned Parenthood–World Population, 810 Seventh Ave., New York, New York 10019.

Perinatal Seminars

Perinatal Resources, Inc., Columbus, Ohio, announces the following Perinatal Seminars:

1. Current Developments in Perinatology, June 14-17, 1979, at Sheraton Islander Inn, Goat Island, Newport, Rhode Island

2. Review of Obstetrics and Gynecology, July 27-29, 1979, at Kings Island Inn, Mason, Ohio

3. A Review Course in Perinatology, September 27-30, 1979, at Fairmont Hotel, New Orleans, Louisiana

4. The Richard Torpin Memorial Postgraduate Course II—Obstetrics, September 30–October 9, 1979, at the Athens Hilton, Athens, Greece

5. Current Concepts in High Risk Obstetrics, January 23-27, 1980, at Aladdin Hotel, Las Vegas, Nevada

For information concerning each of these Seminars, contact Julie Williams, Perinatal Resources, Inc., Gibralter House, 2400 Coventry Road, Columbus, Ohio 43221.

The Treatment of Primary Breast Cancer: Management of Local Disease

The National Cancer Institute of the National Institutes of Health is sponsoring a consensus development conference: The Treatment of Primary Breast Cancer: Management of Local Disease. The conference will be held on June 5, 1979, at the National Institutes of Health Campus in Bethesda, Maryland, in Masur Auditorium (Building 10, Clinical Center) from 8:00 AM to 5:00 PM. Seating is limited and preregistration is required. For further information contact: Ms. Betty Doolittle, NIH-NCI-DCT, Landau Bldg., Room 8C08, Bethesda, Maryland 20014.

Central and Peripheral Regulation of Prolactin Function

An International Symposium on "Central and Peripheral Regulation of Prolactin Function" will be held in Taormina, Italy, October 11-13, 1979, under the auspices of the Italian Society of Endocrinology, the Italian Society of Fertility and Sterility, the Italian Society of Obstetrics and Gynaecology, and the Italian Society of Pharmacology.

For information contact: Umberto Scapagnini, M.D., Department of Pharmacology, Città Universitaria, Via A. Doria, 6, Catania 95100, Italy.

Second Annual Comprehensive Review of Obstetrics and Gynecology

The Second Annual Comprehensive Review of Obstetrics and Gynecology, presented by Baylor College of Medicine, Department of Obstetrics and Gynecology, will be held at the Marriott Hotel at the Astrodome, 2100 S. Braeswood Blvd. at Greenbriar, Houston, Texas 77030, October 26-31, 1979.

For information contact: The Office of Continuing Education, Baylor College of Medicine, Texas Medical Center, Houston, Texas 77030. Telephone: (713) 790-4941.

Fourth Annual Frank R. Lock Symposium in Obstetrics and Gynecology

The Fourth Annual Frank R. Lock Symposium in Obstetrics and Gynecology will be presented April 11-12, 1980, at Babcock Auditorium, Winston-Salem, North Carolina.

For information contact: Division of Continuing Education, 300 S. Hawthorne Road, Bowman Gray School of Medicine, Winston-Salem, North Carolina 27103. Telephone: (919) 727-4450.

One Hundred Fiftieth Anniversary Scholarships

As part of its One Hundred Fiftieth Anniversary Celebration this year, the Rochester Institute of Technology (RIT), in New York, will award individual $1,500 scholarships to 150 lucky babies born on June 12, 1979.

It was on that date 150 years ago that the Rochester Athenaeum, RIT's predecessor, was founded.

Parents of all "anniversary" babies need only to submit a brief letter giving the name of their baby and their home address and telephone number. The first 150 respondents, as determined by postmark of the letters, will be declared winners of the scholarships. However, they also must be admitted to the Institute when ready for college.

A list of alternates will be chosen by the same process.

Funds for the scholarship program in the amount of $225,000—the largest scholarship fund ever awarded at RIT—are being provided by Mr. and Mrs. J. Warren McClure of Key Largo, Florida, and Charlotte, Vermont.

The scholarships will be available starting in 1997, when the recipients are ready for enrollment at RIT. The award winners will be known as the "McClure Scholars." The scholaships are applicable to full-time or part-time/day or evening education, and may be used until 2002.

Parents should send their letters to: RIT McClure Scholars, Rochester Institute of Technology (1829), One Lomb Memorial Dr., Rochester, New York 14623. Deadline for this registration step is October 1, 1979.

The Institute reserves the right to verify the date of birth of the baby. This scholarship offering is void where prohibited by law.

The Institute will announce the names of the lucky 150 winners, and the alternate list during RIT's One Hundred Fiftieth Anniversary Celebration weekend, October 19-21, 1979.

Seventh Annual Convention of The National Intravenous Therapy Association, Inc.

The National Intravenous Therapy Association, Inc., announces its Seventh Annual Convention, to be held June 10-14, 1979, at the Chicago Marriott, Chicago, Illinois.

For information write: NITA Business Office, Steven K. Herlitz, Inc., 850 Third Ave., New York, New York 10022.

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While every precaution is taken to insure accuracy, we cannot guarantee against the possibility of an occasional change or omission in the preparation of this index.

BELLERGAL-S™ TABLETS

Composition: Each Bellergal-S Tablet contains: phenobarbital, USP, central sedative (Warning: May be habit forming), 40.0 mg; Gynergen (ergotamine tartrate, USP) sympathetic inhibitor, 0.6 mg; Bellafoline (levorotatory alkaloids of belladonna, as malates) parasympathetic inhibitor, 0.2 mg.

Properties and Therapeutics: Based on the concept that functional disorders frequently involve hyperactivity of both the sympathetic and parasympathetic nervous systems, the ingredients in Bellergal are combined to provide a balanced preparation designed to correct imbalance of the autonomic nervous system. The integrated action of Bellergal is effected through the combined administration of ergotamine and the levorotatory alkaloids of belladonna, specific inhibitors of the sympathetic and parasympathetic respectively, reinforced by the synergistic action of phenobarbital in dampening the cortical centers.

Indications: Bellergal is employed in the management of disorders characterized by nervous tension and exaggerated autonomic response:

Menopausal disorders with hot flashes, sweats, restlessness and insomnia.

Cardiovascular disorders with palpitation, tachycardia, chest oppression and vasomotor disturbances.

Gastrointestinal disorders with hypermotility, hypersecretion, "nervous stomach," and alternately diarrhea and constipation.

Genitourinary – uterine cramps, etc.

Premenstrual tension.

Interval treatment of *recurrent, throbbing headache.*

Contraindications: Peripheral vascular disease, coronary heart disease, hypertension, impaired hepatic or renal function, sepsis, third trimester of pregnancy and glaucoma. Hypersensitivity to any of the components.

Precautions: Even though the ergotamine tartrate content of this product is extremely low and untoward effects have been rare and insignificant, caution should be exercised if large or prolonged dosage is contemplated, and physicians should be alert to possible peripheral vascular complications in patients highly sensitive to ergot. Due to presence of a barbiturate, may be habit forming.

Side Effects: Blurred vision, dry mouth, flushing, drowsiness occur rarely.

Dosage: Bellergal-S Tablets: One in the morning and one in the evening.

How Supplied: Bellergal-S Tablets (compressed, scored tablets of tricolored pattern: dark green, orange and light lemon yellow) in bottles of 100.

Dorsey LABORATORIES
Division of Sandoz, Inc.
LINCOLN, NEBRASKA 68501

NONHORMONAL therapy for menopausal vasomotor instability is receiving renewed attention.

BELLERGAL-S™

TABLETS



Each Bellergal-S Tablet contains: phenobarbital, USP, central sedative (Warning: May be habit forming), 40.0 mg; Gynergen® (ergotamine tartrate, USP) sympathetic inhibitor, 0.6 mg; Bellafoline® (levorotatory alkaloids of belladonna, as malates) parasympathetic inhibitor, 0.2 mg.

Long clinical experience has established the effectiveness of Bellergal-S Tablets in managing menopausal disorders characterized by exaggerated autonomic response—hot flashes, sweats, restlessness, and insomnia.

Because Bellergal-S reduces autonomi nervous system activity, symptoms of vasomotor instability are eliminated or significantly reduced. *Bellergal-S does not contain estrogen in any form.* That's one reason why it is receiving renewed attention from physicians who wish to avoid the potential complications of estrogen therapy in vasomotor instabili

So when estrogen therapy is undesirable... prescribe Bellergal-S Tablets.

Please see prescribing information on an adjoining page.

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Why the choice is Cu-7®

intrauterine copper contraceptive









1. She wants nonhormonal contraception.
2. She wants to space her family.
3. She smokes.
4. She has passed the "Pill" years.

Freedom—intrauterine contraception is the most convenient of all contraceptive methods.

Comfort—smallest inserter diameter of all IUDs. This means minimal discomfort during insertion.

Cu-7	Lippes Loop® D	Saf-T-Coil® (Nullip)	Saf-T-Coil® (Standard)
3.07 mm.	5.33 mm.	3.76 mm.	4.50 mm.

Security—high efficacy and relatively low incidence of expulsion and medical removal.

(Rates—based on labeling claims—expressed as events per 100 women through 12 months of use for parous women)*	Cu-7[1]	Lippes Loop D[2]	Saf-T-Coil[2]
Pregnancy	1.9	2.7	2.4
Expulsion	5.7	12.7	18.3
Medical Removal	10.9	15.2	15.6

*These rates are derived from separate studies conducted by different investigators in several population groups. Different rates have been reported from other clinical trials.

References: 1. Data on file at Searle Laboratories. 2. Physicians' Desk Reference, Medical Economics Company, Oradell, N.J., 1978, pp. 1216, 1521.

Intrauterine contraception is not appropriate for all women. Please see complete product information prior to use. A brief summary of product information appears on the next page

Description: The plastic component of the Cu-7 is composed of pharmaceutical grade polypropylene homopolymer with barium sulfate added to render it radiopaque. Its shape approximates the number 7. It is substantially smaller than previously available intrauterine devices; the vertical dimension measures 36 mm. and the horizontal, 26 mm.

Coiled around the vertical limb is a pure, virgin electrolytic copper wire providing approximately 200mm^2 of exposed copper surface area. A retrieval thread is fastened to the free end of the vertical limb of the Cu-7.

The Cu-7 is supplied with a simple tubular polypropylene inserter. All components are sterile.

Mode of Action: Available data indicate that the contraceptive effectiveness of the Cu-7 is enhanced by a minute quantity of copper released continuously from the coiled copper into the uterine cavity.

The exact mechanism by which metallic copper enhances the contraceptive effect of an IUD has not been conclusively demonstrated. Various hypotheses have been advanced, the most common being that copper placed in the uterus interferes with enzymatic or other processes that regulate blastocyst implantation.

Animal studies suggest that copper may play an additional role by reduction of sperm transport within the uterine environment.

Indication and Usage: The Cu-7 is indicated for contraception.

Contraindications: The Cu-7 should not be inserted when any of the following conditions exist: pregnancy or suspicion of pregnancy; abnormalities of the uterus resulting in distortion of the uterine cavity; acute pelvic inflammatory disease or a history of repeated pelvic inflammatory disease; postpartum endometritis or infected abortion in the past three months; known or suspected uterine or cervical disease such as hyperplasia or carcinoma including unresolved, abnormal "Pap" smear; vaginal bleeding of unknown etiology; untreated acute cervicitis until infection is controlled; diagnosed Wilson's disease; known or suspected allergy to copper; previous ectopic pregnancy, and significant anemia.

Warnings

1. Pregnancy: (a) Long-term effects. The long-term effects on the offspring of the presence of copper in the uterus when pregnancy occurs with the Cu-7 are unknown.

(b) Septic abortion: Reports have indicated an increased incidence of septic abortion associated in some instances with septicemia, septic shock and death in patients becoming pregnant with an IUD in place. Most of these reports have been associated with the mid-trimester of pregnancy. In some cases, the initial symptoms have been insidious and not easily recognized. If pregnancy should occur with a Cu-7 in situ, the Cu-7 should be removed if the thread is visible or, if removal proves to be or would be difficult, interruption of the pregnancy should be considered and offered to the patient as an option, bearing in mind that the risks associated with an elective abortion increase with gestational age.

(c) Continuation of pregnancy. If the patient chooses to continue the pregnancy and the Cu-7 remains in situ, she must be warned of the increased risk of spontaneous abortion and the increased risk of sepsis, including death. The patient must be closely observed and she must be advised to report immediately all abnormal symptoms, such as flu-like syndrome, fever, abdominal cramping and pain, bleeding, or vaginal discharge, because generalized symptoms of septicemia may be insidious.

2. Ectopic pregnancy: (a) A pregnancy which occurs with an IUD in situ is more likely to be ectopic than a pregnancy occurring without an IUD. Therefore, patients who become pregnant while using a Cu-7 should be carefully evaluated for the possibility of an ectopic pregnancy.

(b) Special attention should be directed to patients with delayed menses, slight metrorrhagia and/or unilateral pelvic pain, and to those patients who wish to interrupt a pregnancy occurring in the presence of a Cu-7, to determine whether ectopic pregnancy has occurred.

3. Pelvic infection: An increased risk of pelvic inflammatory disease associated with the use of IUDs has been reported. While unconfirmed, this risk appears to be greatest for young women who are nulliparous and/or who have a multiplicity of sexual partners. Salpingitis can result in tubal damage and occlusion, thereby threatening future fertility. Therefore, it is recommended that patients be taught to look for symptoms of pelvic inflammatory disease. The decision to use an IUD in a particular case must be made by the physician and patient with the consideration of a possible deleterious effect on future fertility.

Pelvic infection may occur with a Cu-7 in situ and at times result in the development of tubo-ovarian abscesses or general peritonitis. The symptoms of pelvic infection include: new development of menstrual disorders (prolonged or heavy bleeding), abnormal vaginal discharge, abdominal or pelvic pain, dyspareunia, fever. The symptoms are especially significant if they occur following the first two or three cycles after insertion. Appropriate aerobic and anaerobic bacteriologic studies should be done and antibiotic therapy initiated promptly. If the infection does not show marked clinical improvement within 24 to 48 hours, the Cu-7 should be removed and the continuing treatment reassessed on the basis of the results of culture and sensitivity tests.

4. Embedment: Partial penetration or lodging of the Cu-7 in the endometrium or myometrium can result in a difficult removal. This may occur more frequently in smaller uteri. (See removal instructions.)

5. Perforation: Partial or total perforation of the uterine wall or cervix may occur with the use of the Cu-7, usually during insertions into patients sooner than two months after abortion or delivery or in uterine cavities too small for the Cu-7. The possibility of perforation must be kept in mind during insertion and at the time of any subsequent examination. If perforation occurs, laparotomy or laparoscopy should be performed as soon as medically feasible and the Cu-7 removed. Abdominal adhesions, intestinal penetration, intestinal obstruction, and local inflammatory reaction with abscess formation and erosion of adjacent viscera may result if the Cu-7 is left in the peritoneal cavity.

6. Medical diathermy: The use of medical diathermy (short-wave and microwave) in a patient with a metal-containing IUD may cause heat injury to the surrounding tissue. Therefore, medical diathermy to the abdominal and sacral areas should not be used on patients using a Cu-7.

7. Effects of copper: Additional amounts of copper available to the body from the Cu-7 may precipitate symptoms in women with undiagnosed Wilson's disease. The incidence of Wilson's disease is 1 in 200,000.

Precautions

1. Patient counseling: Prior to the insertion the physician, nurse, or other trained health professional must provide the patient with the Patient Brochure. The patient should be given the opportunity to read the brochure and discuss fully any questions she may have concerning the Cu-7 as well as other methods of contraception.

2. Patient evaluation and clinical considerations: a) A complete medical history should be obtained to determine conditions that might influence the selection of an IUD. A physical examination should include a pelvic examination, "Pap" smear, gonorrhea culture and, if indicated, appropriate tests for other forms of venereal disease. The physician should determine that the patient is not pregnant.

(b) The uterus should be carefully sounded prior to the insertion to determine the degree of patency of the endocervical canal and the internal os, and the direction and depth of the uterine cavity. Exercise care to avoid perforation with the sound. DO NOT USE THE Cu-7 INSERTION INSTRUMENT AS A SOUND. In occasional cases, severe cervical stenosis may be encountered. Do not use excessive force to overcome this resistance.

(c) The uterus usually sounds to a depth of 6 to 8 cm. Insertion of a Cu-7 into a uterine cavity measuring less than 6.5 cm. by sounding may increase the incidence of pain, bleeding, partial or complete expulsion, perforation, and possibly pregnancy.

(d) To reduce the possibility of insertion in the presence of an existing undetermined pregnancy, the optimal time for insertion is the latter part of the menstrual flow or one or two days thereafter. The Cu-7 should not be inserted post partum or post abortion until involution of the uterus is complete. The incidence of perforation and expulsion is greater if involution is not complete.

It is, however, necessary to place the Cu-7 as high as possible within the uterine cavity to help avoid partial or complete expulsion that could result in pregnancy.

Since the Cu-7 represents a different design in intrauterine contraception, physicians are cautioned that it is imperative for them to become thoroughly familiar with the instructions for use before attempting placement of the Cu-7.

(e) IUDs should be used with caution in those patients who have an anemia or a history of menorrhagia or hypermenorrhea. Patients experiencing menorrhagia and/or metrorrhagia following IUD insertion may be at risk for the development of hypochromic microcytic anemia. Also, IUDs should be used with caution in patients receiving anticoagulants or having a coagulopathy.

(f) Syncope, bradycardia or other neurovascular episodes may occur during insertion or removal of IUDs, especially in patients with a previous disposition to these conditions.

(g) Patients with valvular or congenital heart disease are more prone to develop subacute bacterial endocarditis than patients who do not have valvular or congenital heart disease. Use of an IUD in these patients may represent a potential source of septic emboli.

(h) Use of an IUD in those patients with acute cervicitis should be postponed until proper treatment has cleared up the infection.

(i) Since the Cu-7 may be partially or completely expelled, patients should be reexamined and evaluated shortly after the first postinsertion menses, but definitely within three months after insertion. Thereafter annual examination with appropriate medical and laboratory evaluation should be carried out. The Cu-7 should be replaced every three years.

(j) The patient should be told that some bleeding or cramps may occur during the first few weeks after insertion, but if these symptoms continue or are severe she should report them to her physician. She should be instructed on how to check after each menstrual period to make certain that the thread still protrudes from the cervix and cautioned that there is no contraceptive protection if the Cu-7 has been expelled. She should also be cautioned not to dislodge the Cu-7 by pulling on the thread. If a partial expulsion occurs, removal is indicated and a new Cu-7 may be inserted. The patient should be told to return within three years for removal of the Cu-7 and for replacement if desired.

(k) A copper-induced urticarial allergic skin reaction may develop in women using a copper-containing IUD. If symptoms of such an allergic response occur, the patient should be instructed to tell the consulting physician that a copper-containing device is being used.

(l) The Cu-7 should be removed for the following medical reasons: menorrhagia and/or metrorrhagia producing significant anemia; uncontrolled pelvic infection; intractable pain often aggravated by intercourse, dyspareunia; pregnancy, if the thread is visible; endometrial or cervical malignancy; uterine or cervical perforation; or any indication of partial expulsion.

(m) If the retrieval thread cannot be visualized it may have retracted into the uterus or have been broken off, or the Cu-7 may have been expelled. Localization usually may be made by feeling with a probe; if not, x-ray or sonography can be used. When the physician elects to recover a Cu-7 with the thread not visible, the removal instructions should be considered.

(n) If any patient with a Cu-7 suddenly develops overt clinical hepatitis or abnormal liver function tests, appropriate diagnostic procedures should be initiated.

Adverse Reactions: Perforations of uterus and cervix have occurred. Perforation into the abdomen has been followed by abdominal adhesions, intestinal penetration, intestinal obstruction, local inflammatory reaction with abscess formation and erosion of adjacent viscera. Pregnancy has occurred with the Cu-7 in situ and when the Cu-7 has been partially or completely expelled.

The incidence of spontaneous abortion, when conception occurs with intrauterine devices in situ, appears to be increased over that in unprotected women. Insertion cramping, usually of no more than a few seconds duration, may occur; however, some women may experience residual cramping for several hours or even days. Intermenstrual spotting or bleeding or prolonged or increased menstrual flow may occur.

Pelvic infection including salpingitis with tubal damage or occlusion has been reported. This may result in future infertility. Complete or partial expulsion of the Cu-7 may sometimes occur, particularly in those patients with uteri measuring less than 6.5 cm. by sounding. Urticarial allergic skin reaction may occur. The following complaints have also been reported with IUDs although their relation to the Cu-7 has not been established: amenorrhea or delayed menses, backaches, cervical erosion, cystic masses in the pelvis, vaginitis, leg pain or soreness, weight loss or gain, nervousness, dyspareunia, cystitis, endometritis, septic abortion, septicemia, leukorrhea, ectopic pregnancy, difficult removal, uterine embedment, anemia, pain, neurovascular episodes including bradycardia and syncope secondary to insertion, dysmenorrhea, and fragmentation of the IUD.

Directions for Use: The Cu-7 is to be placed within the uterine cavity. See the Procedure for Insertion for two insertion techniques.

The small diameter of the Cu-7 facilitates easy insertion in nulligravidous and nulliparous, as well as parous women. The optimal time of insertion is during the latter part of the menstrual flow or one or two days thereafter. The cervical canal is relatively more patent at this time, and there is little chance that the patient may be pregnant.

Present information indicates that efficacy is retained for 36 months. There is no evidence that contraceptive efficacy decreases with time up to three years of use, but until adequate data indicating a longer effective life become available, the Cu-7 must be removed within 36 months from the date of insertion and a new one inserted if desired. If partial expulsion occurs, removal is indicated, and a new Cu-7 may be inserted. Removal of the Cu-7 may also be indicated in the event of heavy or persistent bleeding.

The physician should become thoroughly familiar with the instructions for use before attempting insertion or removal of the Cu-7.

Clinical Efficacy: In clinical trials of the Cu-7 conducted by Searle Laboratories, use effectiveness was determined as follows for parous and nulliparous women, as tabulated by the life table method. (Rates are expressed as cumulative events per 100 women through 12, 24, and 36 months of use.)

This experience encompasses 387,131 woman-months of use, including 12 months for 11,517 women, 24 months for 7,895, and 36 months for 3,661.

	12 Months		24 Months		36 Months	
	Parous	Nulliparous	Parous	Nulliparous	Parous	Nulliparous
Pregnancy	1.9	1.7	2.9	2.6	3.4	3.4

How Supplied

Available in cartons of 6, 30 and 100 sterile units (Cu-7 with an inserter) and sufficient patient leaflets and identification cards.

Please see complete product labeling for additional information, including insertion and removal instructions.

SEARLE **Searle Laboratories**
Division of Searle Pharmaceuticals Inc.
Box 5110, Chicago, Illinois 60680

Cu-7® intrauterine copper contraceptive

—the leading IUD

8B4



How much estrogen does it really take to control nature?

A lot less than everyone once thought. Just a few years ago, a 50-mcg dosage was considered low. Today, there's an effective combination oral contraceptive containing 30 mcg of estrogen: Loestrin 1.5/30.

In spite of a 40% reduction in the dose of estrogen, efficacy of Loestrin 1.5/30 is considered comparable to that of combination oral contraceptives containing higher levels of estrogen.

Irregular bleeding is somewhat more frequent with Loestrin 1.5/30 than with combinations containing larger doses of estrogen. With continued use, however, the frequency decreases.

And if you're concerned about your patients' intake of estrogen over an extended period of time, Loestrin 1.5/30 contains 30 mcg of ethinyl estradiol, so patient exposure to estrogen is reduced.

LOESTRIN® 1.5/30

(1.5 mg norethindrone acetate and 30 mcg ethinyl estradiol tablets, USP)

a 30-mcg alternative to higher estrogen

isualization of
ammalian ovulation.
opyright © 1971, by
ine-Science Co., Ltd.,
apan.

See opposite page for prescribing information.

Brief Summary of Prescribing Information
LOESTRIN® 1.5/30
(1.5 mg norethindrone acetate and 30 mcg ethinyl estradiol tablets, USP) See section under Special Notes on Administration and How Supplied.

DESCRIPTION
Loestrin 1.5/30 Products are progestogen-estrogen combinations.

INDICATION AND USAGE
Loestrin 1.5/30 Products are indicated for the prevention of pregnancy in women who elect to use oral contraceptives.

In clinical trials with Loestrin 1.5/30 involving 17,139 therapy cycles, there was a pregnancy rate of 0.49 per 100 woman years.

Dose-related risk of thromboembolism from oral contraceptives: Studies have shown a positive association between the dose of estrogens in oral contraceptives and the risk of thromboembolism. It is prudent and in keeping with good principles of therapeutics to minimize exposure to estrogen. The oral contraceptive prescribed for any given patient should be that product which contains the least amount of estrogen that is compatible with an acceptable pregnancy rate and patient acceptance.

CONTRAINDICATIONS
1. Thrombophlebitis or thromboembolic disorders
2. A past history of deep-vein thrombophlebitis or thromboembolic disorders
3. Cerebral vascular or coronary artery disease
4. Known or suspected carcinoma of the breast
5. Known or suspected estrogen-dependent neoplasia
6. Undiagnosed abnormal genital bleeding
7. Known or suspected pregnancy (See No. 5 under WARNINGS.)

WARNINGS

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

The use of oral contraceptives is associated with increased risk of several serious conditions including thromboembolism, stroke, myocardial infarction, hepatic adenoma, gallbladder disease, and hypertension. Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks.

1. *Thromboembolic Disorders and Other Vascular Problems:* An increased risk of thromboembolic and thrombotic disease associated with the use of oral contraceptives is well-established. Studies have demonstrated an increased risk of fatal and nonfatal venous thromboembolism and stroke, both hemorrhagic and thrombotic.

Cerebrovascular disorders: In a collaborative study in women with and without predisposing causes, it was estimated that the risk of hemorrhagic stroke was 2.0 times greater in users than nonusers, and the risk of thrombotic stroke was 4.0 to 9.5 times greater.

Myocardial infarction: An increased risk of myocardial infarction associated with oral contraceptives has been reported confirming a previously suspected association. These studies found that the greater the number of underlying risk factors (cigarette smoking, hypertension, hypercholesterolemia, obesity, diabetes, history of preeclamptic toxemia) for coronary artery disease, the higher the risk of developing myocardial infarction, regardless of whether the patient was an oral contraceptive user or not. Oral contraceptives, however, were found to be a clear additional risk factor.

It has been estimated that users who do not smoke (smoking is considered a major predisposing condition to myocardial infarction) are about twice as likely to have a fatal myocardial infarction as nonusers who do not smoke. Oral contraceptive users who are smokers have about a fivefold increased risk of fatal infarction compared to users who do not smoke, but about a tenfold to twelvefold increased risk compared to nonusers who do not smoke. The amount of smoking is also an important factor.

Risk of dose: In an analysis of data, British investigators concluded that the risk of thromboembolism including coronary thrombosis is directly related to the dose of estrogen used in oral contraceptives; however, the quantity of estrogen may not be the sole factor involved.

Estimate of excess mortality from circulatory diseases: The risk of diseases of the circulatory system is concentrated in older women, in those with a long duration of use, and in cigarette smokers.

A study of available data from a variety of sources concluded that the mortality associated with all methods of birth control is low and below that associated with childbirth, with the exception of oral contraceptives in women over 40 who smoke.

The risk of thromboembolic and thrombotic diseases associated with oral contraceptives increases with age after approximately age 30 and, for myocardial infarction, is further increased by hypertension, hypercholesterolemia, obesity, diabetes, or history of preeclamptic toxemia, and especially by cigarette smoking.

The physician and the patient should be alert to the earliest manifestations of thromboembolic and thrombotic disorders. Should any occur or be suspected, the drug should be discontinued immediately.

A fourfold to sixfold increased risk of postsurgery thromboembolic complications has been reported in users. If feasible, oral contraceptives should be discontinued at least four weeks before surgery of a type associated with an increased risk of thromboembolism or prolonged immobilization.

2. *Ocular lesions:* Neuro-ocular lesions, such as optic neuritis or retinal thrombosis, have been associated with the use of oral contraceptives. Discontinue the oral contraceptive if there is unexplained sudden or gradual, partial, or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal vascular lesions.

3. *Carcinoma:* Long-term continuous administration of estrogen in certain animal species increases the frequency of carcinoma of the breast, cervix, vagina, and liver.

In humans, an increased risk of endometrial carcinoma associated with the prolonged use of exogenous estrogen in postmenopausal women has been reported. However, there is no evidence suggesting increased risk of endometrial cancer in users of conventional combination or progestogen-only oral contraceptives.

Studies found no evidence of increase in breast cancer in women taking oral contraceptives; however, an excess risk in users with documented benign breast disease was reported.

There is no confirmed evidence of an increased risk of cancer associated with oral contraceptives. Close clinical surveillance of users is, nevertheless, essential. In cases of undiagnosed persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be taken to rule out malignancy. Women with a strong family history of breast cancer, or who have breast nodules, fibrocystic disease, or abnormal mammograms, should be monitored with particular care.

4. *Hepatic Tumors:* Benign hepatic adenomas have been found to be associated with oral contraceptives. Because hepatic adenomas may rupture and may cause death through intra-abdominal hemorrhage, they should be considered in women presenting abdominal pain and tenderness, abdominal mass, or shock.

A few cases of hepatocellular carcinoma have been reported in women taking oral contraceptives. The relationship of these drugs to this type of malignancy is not known at this time.

5. *Usage in or Immediately Preceding Pregnancy: Birth Defects in Offspring, and Malignancy in Female Offspring:* During early pregnancy, female sex hormones may seriously damage the offspring.

An increased risk of congenital anomalies, including heart defects and limb defects, has been reported with the use of oral contraceptives in pregnancy.

There is some evidence that triploidy and possibly other types of polyploidy are increased among abortuses from women who become pregnant soon after ceasing oral contraceptives.

Pregnancy should be ruled out before continuing an oral contraceptive in any patient who has missed two consecutive menstrual periods. If the patient has not adhered to the schedule, the possibility of pregnancy should be considered at the time of the first missed period, and oral contraceptives should be withheld until pregnancy has been ruled out. If pregnancy is confirmed, the patient should be apprised of the potential risks to the fetus and the advisability of continuation of the pregnancy should be discussed.

Women who discontinue oral contraceptives with the intent of becoming pregnant should use an alternate form of contraception for a period of time before attempting to conceive.

Administration of progestogen-only or progestogen-estrogen combinations to induce withdrawal bleeding should not be used as a test of pregnancy.

6. *Gallbladder Disease:* Studies report an increased risk of surgically confirmed gallbladder disease in users of oral contraceptives.

7. *Carbohydrate and Lipid Metabolic Effects:* Because decreased glucose tolerance has been observed in a significant percentage of patients, prediabetic and diabetic patients should be carefully observed while receiving oral contraceptives.

An increase in triglycerides and total phospholipids has been observed.

8. *Elevated Blood Pressure:* An increase in blood pressure has been reported in patients receiving oral contraceptives. The prevalence in users increases with longer exposure. Age is also strongly correlated with development of hypertension. Women who previously have had hypertension during pregnancy may be more likely to develop elevation of blood pressure.

9. *Headache:* Onset or exacerbation of migraine or development of headache of a new pattern which is recurrent, persistent, or severe, requires discontinuation of oral contraceptive

10. *Bleeding Irregularities:* Breakthrough bleeding, spotting, and amenorrhea are frequent reasons for patients discontinuing oral contraceptives. In breakthrough bleeding, nonfunctional causes should be borne in mind. In undiagnosed abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy.

Women with a past history of oligomenorrhea or secondary amenorrhea, or young women without regular cycles should be advised that they may have a tendency to remain anovulatory or to become amenorrheic after discontinuation of oral contraceptives.

11. *Ectopic Pregnancy:* Ectopic as well as intrauterine pregnancy may occur in contraceptive failures.

12. *Breast Feeding:* Oral contraceptives may interfere with lactation. Furthermore, a small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs.

PRECAUTIONS
1. A complete medical and family history should be taken prior to the initiation of oral contraceptives. The pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen, and pelvic organs, including Papanicolaou smear and relevant laboratory tests. As a general rule, oral contraceptives should not be prescribed for longer than one year without another examination.

2. Preexisting uterine leiomyomata may increase in size.

3. Patients with a history of psychic depression should be carefully observed and the drug discontinued if depression recurs to a serious degree.

4. Oral contraceptives may cause fluid retention and should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated.

5. Patients with a past history of jaundice during pregnancy have an increased risk of recurrence of jaundice. If jaundice develops, the medication should be discontinued.

6. Steroid hormones may be poorly metabolized and should be administered with caution in patients with impaired liver function.

7. Users may have disturbances in normal tryptophan metabolism, which may result in a relative pyridoxine deficiency.

8. Serum folate levels may be depressed.

9. The pathologist should be advised of oral contraceptive therapy when relevant specimens are submitted.

10. Certain endocrine and liver function tests and blood components may be affected.
(a) Increased sulfobromophthalein retention. (b) Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability (c) Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone. (d) Decreased pregnanediol excretion. (e) Reduced response to metyrapone test.

Drug interactions: Reduced efficacy and increased incidence of breakthrough bleeding have been associated with concomitant use of rifampin and an association has been suggested with barbiturates, phenylbutazone, phenytoin sodium, and ampicillin.

ADVERSE REACTIONS
An increased risk of the following serious adverse reactions has been associated with oral contraceptives.

Thrombophlebitis; Pulmonary embolism; Coronary thrombosis; Cerebral thrombosis; Cerebral hemorrhage; Hypertension; Gallbladder disease; Benign hepatomas; Congenital anomalies.

There is evidence of an association between the following conditions and the use of oral contraceptives, although additional confirmatory studies are needed. Mesenteric thrombosis, Neuro-ocular lesions, eg, retinal thrombosis and optic neuritis.

The following adverse reactions have been reported in patients receiving oral contraceptives and are believed to be drug-related: Nausea and/or vomiting, usually the most common adverse reactions, occur in approximately 10 percent or less of patients during the first cycle. Other reactions, as a general rule, are seen much less frequently or only occasionally: gastrointestinal symptoms; breakthrough bleeding; spotting; change in menstrual flow; dysmenorrhea; amenorrhea during and after treatment; temporary infertility after discontinuance of treatment; edema; chloasma or melasma; breast changes; change in weight; change in cervical erosion and cervical secretion; possible diminution in lactation when given immediately post partum; cholestatic jaundice; migraine; increase in size of uterine leiomyomata; rash (allergic); mental depression; reduced tolerance to carbohydrates; vaginal candidiasis; change in corneal curvature; intolerance to contact lenses.

The following adverse reactions have been reported and the association has been neither confirmed nor refuted.

Premenstrual-like syndrome; cataracts; changes in libido; chorea; changes in appetite; cystitis-like syndrome; headache; nervousness; dizziness; hirsutism; loss of scalp hair; erythema multiforme; erythema nodosum; hemorrhagic eruption; vaginitis; porphyria.

Special Notes on Administration
Loestrin 21 1.5/30 (1.5 mg norethindrone acetate and 30 mcg ethinyl estradiol tablets, USP)—Menstruation usually begins two or three days, but may begin as late as the fourth or fifth day, after discontinuing medication.

Loestrin Fe 1.5/30—Menstruation usually begins two or three days, but may begin as late as the fourth or fifth day, after the brown ferrous fumarate tablets have been started.

Because of the relatively low estrogenic content, Loestrin 1.5/30 is not a good cyclic regulator. There are patients whose inherent hormone balance will require larger amounts of estrogen than that contained in Loestrin 1.5/30 to achieve cyclic regularity. These patients experience altered bleeding patterns, which do not conform to treatment schedules.

The physician should be alert to the fact that the irregular bleeding patterns could mask bleeding from organic cause, and appropriate diagnostic measures should be taken if the bleeding persists or continues after changing to a higher estrogen-content product.

After several months, bleeding may be reduced to a virtual absence; reduced flow may be a result of medication and not indicative of pregnancy.

HOW SUPPLIED
Loestrin Fe 1.5/30 is available in compacts each containing 21 green tablets and 7 brown tablets. Each green tablet contains 1.5 mg of norethindrone acetate and 30 mcg of ethinyl estradiol. Each brown tablet contains 75 mg of ferrous fumarate. Available in packages of five compacts and packages of five refills.

Loestrin 21 1.5/30 is available in compacts each containing 21 tablets. Each green tablet contains 1.5 mg of norethindrone acetate and 30 mcg of ethinyl estradiol. Available in packages of five compacts and packages of five refills.

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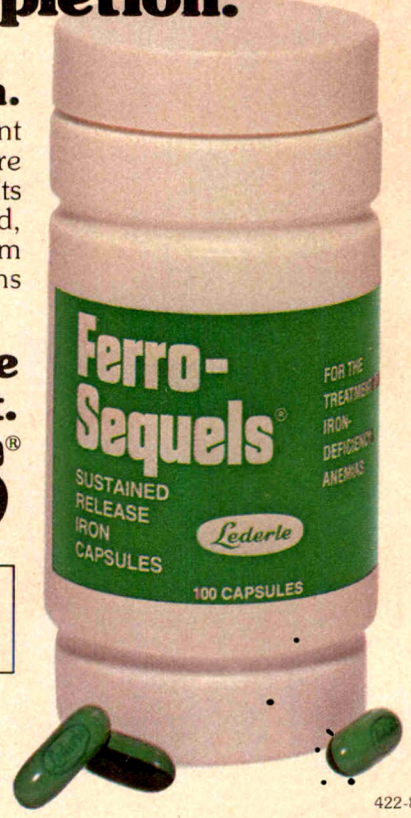
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[1]First Health and Nutrition Survey, HEW Pub. No. (HRA) 74-1219-1.
[2]Herbert, V.—Current Concepts in Nutrition 5. 79 (1977)

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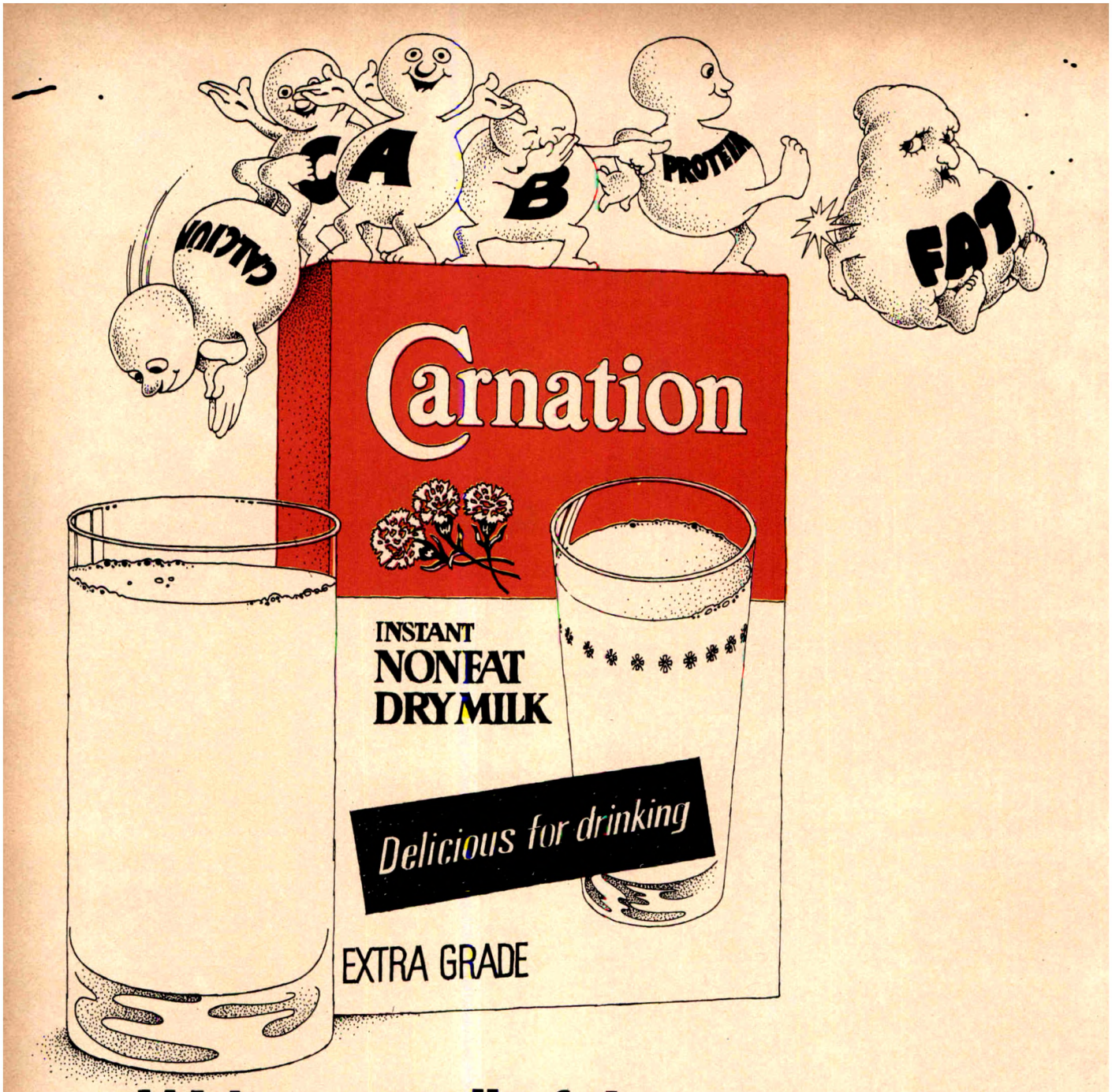
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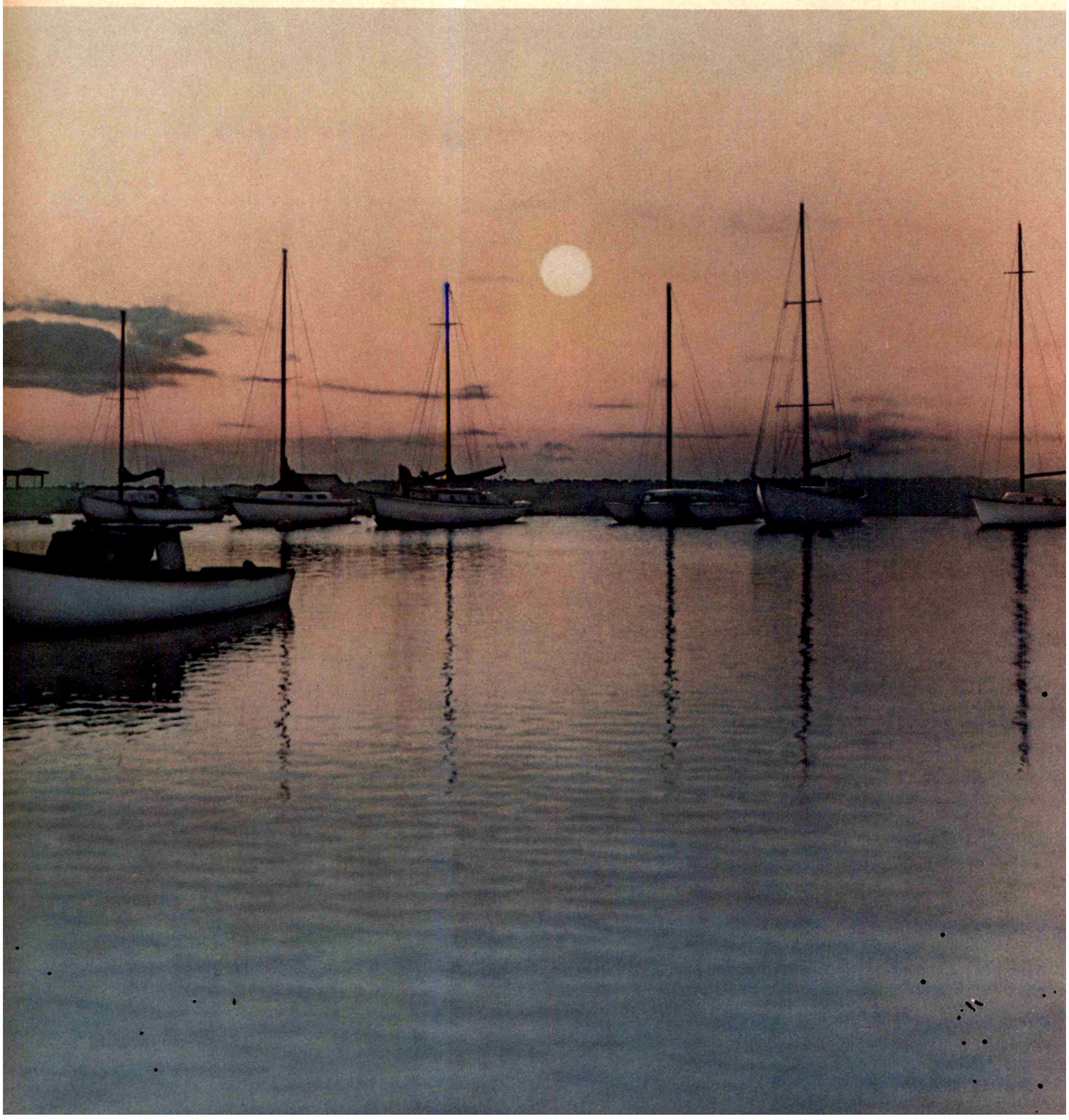
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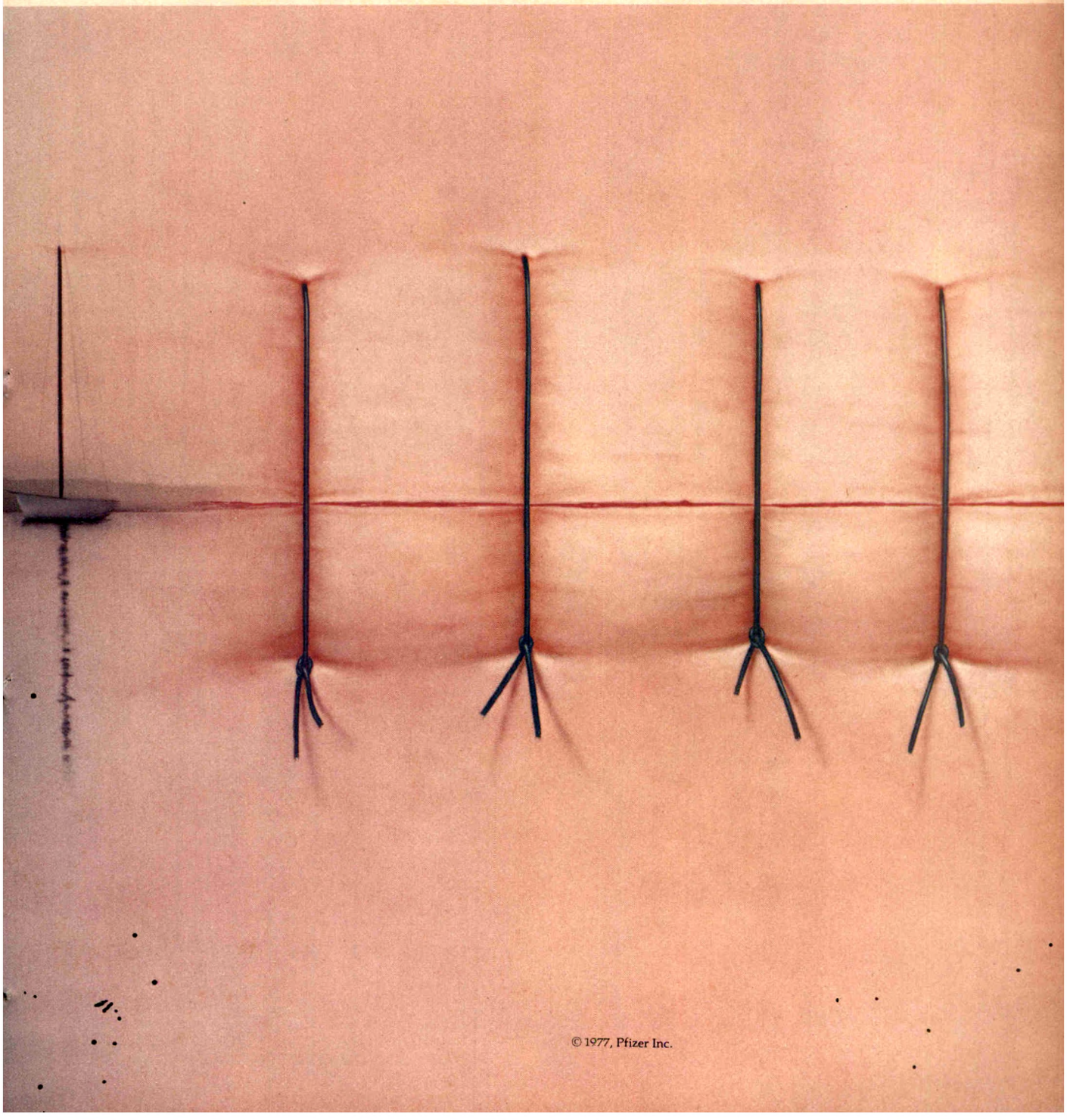


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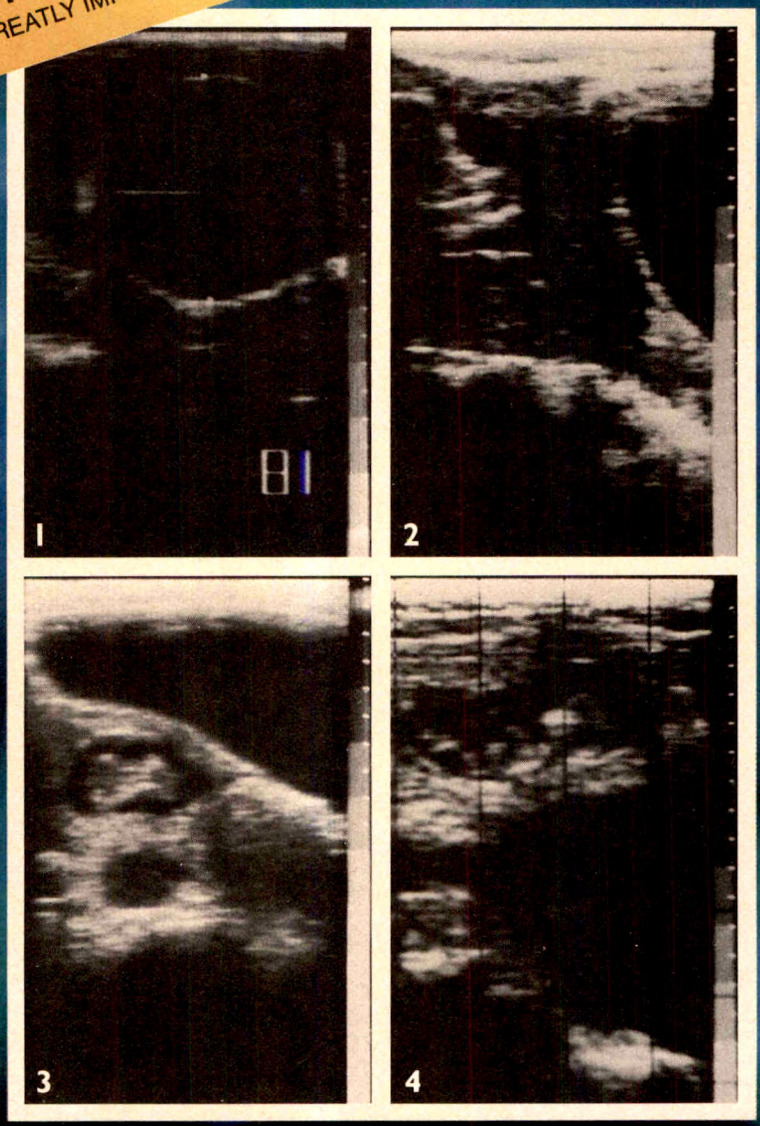
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*Queenan, J.T., Contemp. Ob. Gyn. 9:10, March 1977.

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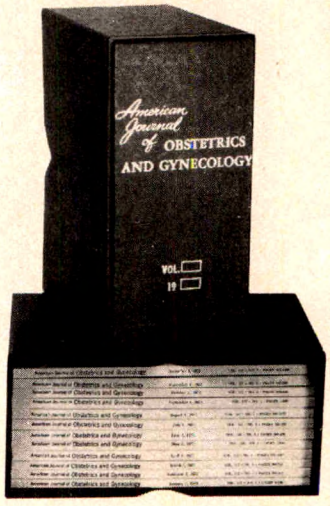
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INDICATION: CONTRACEPTION. The pregnancy rate in women using conventional combination oral contraceptives (containing 35 mcg or more of ethinyl estradiol or 50 mcg or more of mestranol) is generally reported as less than one pregnancy per 100 woman-years of use. Slightly higher rates (somewhat more than one pregnancy per 100 woman-years of use) are reported for some combination products containing 35 mcg or less of ethinyl estradiol, and rates on the order of three pregnancies per 100 woman-years are reported for the progestogen-only oral contraceptives. Table 1 gives ranges of pregnancy rates reported in the literature for other means of contraception. The efficacy of these means of contraception (except the IUD) depends upon the degree of adherence to the method.

Table 1: Pregnancies Per 100 Women-Years. IUD, less than 1-6; Diaphragm with spermicidal product (creams or jellies), 2-20; Condom, 3-36; Aerosol foams, 2-29; Jellies and creams, 4-36; Periodic abstinence (rhythm) all types, less than 1-47; 1. Calendar method, 14-47; 2. Temperature method, 1-20; 3. Temperature method—intercourse only in postovulatory phase, less than 1-7; 4. Mucus method, 1-25; No contraception, 60-80. **DOSE-RELATED RISK OF THROMBOEMBOLISM FROM ORAL CONTRACEPTIVES:** Two studies have shown a positive association between the dose of estrogens in oral contraceptives and the risk of thromboembolism. For this reason, it is prudent and in keeping with good principles of therapeutics to minimize exposure to estrogen. The oral contraceptive product prescribed for any given patient should be that product which contains the least amount of estrogen that is compatible with an acceptable pregnancy rate and patient acceptance. It is recommended that new acceptors of oral contraceptives be started on preparations containing .05 mg or less of estrogen.

CONTRAINDICATIONS: Oral contraceptives should not be used in women with any of the following conditions: 1. Thrombophlebitis or thromboembolic disorders. 2. A past history of deep vein thrombophlebitis or thromboembolic disorders. 3. Cerebral vascular or coronary artery disease. 4. Known or suspected carcinoma of the breast. 5. Known or suspected estrogen-dependent neoplasia. 6. Undiagnosed, abnormal genital bleeding. 7. Known or suspected pregnancy (see WARNINGS, No. 5).

WARNINGS

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

The use of oral contraceptives is associated with increased risk of several serious conditions including thromboembolism, stroke, myocardial infarction, hepatic adenoma, gallbladder disease, hypertension. Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks.

1. THROMBOEMBOLIC DISORDERS AND OTHER VASCULAR PROBLEMS. An increased risk of thromboembolic and thrombotic disease associated with the use of oral contraceptives is well established. Four principal studies in Great Britain and three in the United States have demonstrated an increased risk of fatal and nonfatal venous thromboembolism and stroke, both hemorrhagic and thrombotic. These studies estimate that users of oral contraceptives are 4 to 11 times more likely than nonusers to develop these diseases without evident cause. Overall excess mortality due to pulmonary embolism or stroke is on the order of 1.0 to 3.5 deaths annually per 100,000 users and increases with age. **CEREBROVASCULAR DISORDERS:** In a collaborative American study of cerebrovascular disorders in women with and without predisposing causes, it was estimated that the risk of hemorrhagic stroke was 2.0 times greater in users than in nonusers and the risk of thrombotic stroke was 4.0 to 9.5 times greater in users than in nonusers.

MYOCARDIAL INFARCTION: An increased risk of myocardial infarction associated with the use of oral contraceptives has been reported confirming a previously suspected association. These studies, conducted in the United Kingdom, found, as expected, that the greater the number of underlying risk factors for coronary artery disease (cigarette smoking, hypertension, hypercholesterolemia, obesity, diabetes, history of preeclamptic toxemia), the higher the risk of developing myocardial infarction, regardless of whether the patient was an oral contraceptive user or not. Oral contraceptives, however, were found to be a clear additional risk factor. The annual excess case rate (increased risk) of myocardial infarction (fatal and nonfatal) in oral contraceptive users was estimated to be approximately 7 cases per 100,000 women users in the 30-39 age group and 67 cases per 100,000 women users in the 40-44 age group. In terms of relative risk, it has been estimated that oral contraceptive users who do not smoke (smoking is considered a major predisposing condition to myocardial infarction) are about twice as likely to have a fatal myocardial infarction as nonusers who do not smoke. Oral contraceptive users who are also smokers have about a 5-fold increased risk of fatal infarction compared to users who do not smoke, but about a 10-to 12-fold increased risk compared to nonusers who do not smoke. Furthermore, the amount of smoking is also an important factor. In determining the importance of these relative risks, however, the baseline rates for various age groups must be given serious consideration. The importance of other predisposing conditions mentioned above in determining relative and absolute risks has not as yet been quantified; it is quite likely that the same synergistic action exists, but perhaps to a lesser extent. **Risk of Dose:** In an analysis of data derived from several national adverse reaction reporting systems, British investigators concluded that the risk of thromboembolism including coronary thrombosis is directly related to the dose of estrogen used in oral contraceptives. Preparations containing 100 mcg or more of estrogen were associated with a higher risk of thromboembolism than those containing 50-80 mcg of estrogen. Their analysis did suggest, however, that the quantity of estrogen may not be the sole factor involved. This finding has been confirmed in the United States. Careful epidemiological studies to determine the degree of thromboembolic risk associated with progestogen-only oral contraceptives have not been performed. Cases of thromboembolic disease have been reported in women using these products, and they should not be presumed to be free of excess risk. The risk of thromboembolic and thrombotic disorders, in both users and nonusers of oral contraceptives, increases with age. Oral contraceptives are, however, an independent risk factor for these events. **ESTIMATE OF EXCESS MORTALITY FROM CIRCULATORY DISEASES:** A large prospective study carried out in the United Kingdom estimated the mortality rate per 100,000 women per year from diseases of the circulatory system for users and nonusers of oral contraceptives according to age, smoking habits, and duration of use. The overall excess death rate annually from circulatory diseases for oral contraceptive users was estimated to be 20 per 100,000 (ages 15-34—5/100,000; ages 35-44—33/100,000; ages 45-49—140/100,000), the risk being concentrated in older women, in those with a long duration of use, and in cigarette smokers. It was not possible, however, to examine the interrelationships of age, smoking, and duration of use, nor to compare the effects of continuous versus intermittent use. Although the study showed a 10-fold increase in death due to circulatory diseases in users for five or more years, all of these deaths occurred in women 35 or older. Until larger numbers of women under 35 with continuous use for five or more years are available, it is not possible to assess the magnitude of the relative risk for this younger age group. This study reports that the increased risk of circulatory diseases may persist after the pill is discontinued. Another study published at the same time confirms a previously reported increase of mortality in pill users from cardiovascular disease. The available data from a variety of sources have been analyzed to estimate the risk of death associated with various methods of contraception. The estimates of risk of death for each method include the combined risk of the contraceptive method (e.g., thromboembolic and thrombotic disease in the case of oral contraceptives) plus the risk attributable to pregnancy or abortion in the event of method failure. This latter risk varies with the effectiveness of the contraceptive method. The findings of this analysis are shown in Figure 1 below. The study concluded that the mortality associated with all methods of birth control is low and below that associated with childbirth, with the exception of oral contraceptives in women over 40 who smoke. (The rates given for pill only/smokers for each age group are for smokers as a class. For "heavy" smokers [more than 15 cigarettes a day], the rates given would be about double; for "light" smokers [less than 15 cigarettes a day], about 50 percent.) The mortality associated with oral contraceptive use in nonsmokers over 40 is higher than with any other method of contraception in that age group. The lowest mortality is associated with the condom or diaphragm backed up by early abortion. The risk of thromboembolic and thrombotic disease associated with oral contraceptives increases with age after approximately age 30 and, for myocardial infarction, is further increased by hypertension, hypercholesterolemia, obesity, diabetes, or history of preeclamptic toxemia and especially by cigarette smoking. The risk of myocardial infarction in oral contraceptive users is substantially increased in women age 40 and over, especially those with other risk factors. Based on the data currently available, the following chart gives a gross estimate of the risk of death from circulatory disorders associated with the use of oral contraceptives:

SMOKING HABITS AND OTHER PREDISPOSING CONDITIONS—RISK ASSOCIATED WITH USE OF ORAL CONTRACEPTIVES

Age	Below 30	30-39	40+	
Heavy smokers	C	B	A	A—Use associated with very high risk.
Light smokers	D	C	B	B—Use associated with high risk.
Nonsmokers (no predisposing conditions)	D	C,D	C	C—Use associated with moderate risk.
Nonsmokers (other predisposing conditions)	C	C,B	B,A	D—Use associated with low risk.

The physician and the patient should be alert to the earliest manifestations of thromboembolic and thrombotic disorders (e.g., thrombophlebitis, pulmonary embolism, cerebrovascular insufficiency, coronary occlusion, retinal thrombosis, and mesenteric thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately. A four- to six-fold increased risk of postsurgery thromboembolic complications has been reported in oral contraceptive users. If feasible, oral contraceptives should be discontinued at least four weeks before surgery of a type associated with an increased risk of thromboembolism or prolonged immobilization. 2. OCULAR LESIONS. There have been reports of neuro-ocular lesions such as optic neuritis or retinal thrombosis associated with the use of oral contraceptives. Discontinue oral contraceptive medication if there is unexplained, sudden or gradual, partial or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal vascular lesions and institute appropriate diagnostic and therapeutic measures. 3. CARCINOMA. Long-term continuous administration of either natural or synthetic estrogen in certain animal species increases the frequency of carcinoma of the breast, cervix, vagina, and liver. Certain synthetic progestogens, none currently contained in oral contraceptives, have been noted to increase the incidence of mammary nodules, benign and malignant, in dogs. In humans, three case control studies have reported an increased risk of endometrial carcinoma associated with the prolonged use of exogenous estrogen in postmenopausal women. One publication reported on the first 21 cases submitted by physicians to a registry of cases of adenocarcinoma of the endometrium in women under 40 on oral contraceptives. Of the cases found in women without predisposing risk factors for adenocarcinoma of the endometrium (e.g., irregular bleeding at the time oral contraceptives were first given, polycystic ovaries), nearly all occurred in women who had used a sequential oral contraceptive. These products are no longer marketed. No evidence has been reported suggesting an increased risk of endometrial cancer in users of conventional combination or progestogen-only oral contraceptives. Several studies have found no increases in breast cancer in women taking oral contraceptives or estrogens. One study, however, while also noting no overall increased risk of breast cancer in women treated with oral contraceptives, found an excess risk in the subgroups of oral contraceptive users with documented benign breast disease. A reduced occurrence of benign breast tumors in users of oral contraceptives has been well-documented. In summary, there is at present no confirmed evidence from human studies of an increased risk of cancer associated with oral contraceptives. Close clinical surveillance of all women taking oral contraceptives is, nevertheless, essential. In all cases of undiagnosed persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be taken to rule out malignancy. Women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease or abnormal mammograms should be monitored with particular care if they elect to use oral contraceptives instead of other methods of contraception. *Trademark

Women, by regimen of control and age of woman.

	15-19	20-24	25-29	30-34	35-39	40-44
No method	5.5	5.2	7.1	14.0	19.3	21.9
Abortion only	2.3	2.5	2.5	5.2	9.8	6.6
Pill only-nonsmokers	1.3	1.4	1.4	2.2	4.5	3.1
Pill only-smokers	1.5	1.6	1.6	10.8	13.4	58.9
IUDs only	1.1	1.2	1.2	1.4	1.6	1.4
Traditional contraception only	1.1	1.4	1.9	3.7	4.7	4.0
Traditional contraception and abortion	0.3	0.4	0.4	0.8	1.4	0.8

4. HEPATIC TUMORS. Benign hepatic adenomas have been found to be associated with the use of oral contraceptives. One study showed that oral contraceptive formulations with high hormonal potency were associated with a higher risk than lower potency formulations. Although benign, hepatic adenomas may rupture and may cause death through intra-abdominal hemorrhage. This has been reported in short-term as well as long-term users of oral contraceptives. Two studies relate risk with duration of use of the contraceptive, the risk being much greater after four or more years of oral contraceptive use. While hepatic adenoma is a rare lesion, it should be considered in women presenting abdominal pain and tenderness, abdominal mass or shock. A few cases of hepatocellular carcinoma have been reported in women taking oral contraceptives. The relationship of these drugs to this type of malignancy is not known at this time. 5. USE IN OR IMMEDIATELY PRECEDING PREGNANCY, BIRTH DEFECTS IN OFFSPRING, AND MALIGNANCY IN FEMALE OFFSPRING. The use of female sex hormones—both estrogenic and progestational agents—during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a nonsteroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare. This risk has been estimated to be on the order of 1 to 4 in 1000 exposures. Although there is no evidence at the present time that oral contraceptives further enhance the risk of developing this type of malignancy, such patients should be monitored with particular care if they elect to use oral contraceptives instead of other methods of contraception. Furthermore, a high percentage of such exposed women (from 30 to 90%) have been found to have epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether this condition is a precursor of vaginal malignancy. Male children so exposed may develop abnormalities of the urogenital tract. Although similar data are not available with the use of other estrogens, it cannot be presumed that they would not induce similar changes. An increased risk of congenital anomalies, including heart defects and limb defects, has been reported with the use of sex hormones, including oral contraceptives, in pregnancy. One case control study has estimated a 4.7-fold increase in risk of limb-reduction defects in infants exposed in utero to sex hormones (oral contraceptives, hormonal withdrawal tests for pregnancy or attempted treatment for threatened abortion). Some of these exposures were very short and involved only a few days of treatment. The data suggest that the risk of limb-reduction defects in exposed fetuses is somewhat less than one in 1,000 live births. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well-controlled studies that progestogens are effective for these uses. There is some evidence that triploidy and possibly other types of polyploidy are increased among abortuses from women who become pregnant soon after ceasing oral contraceptives. Embryos with these anomalies are virtually always aborted spontaneously. Whether there is an overall increase in spontaneous abortion of pregnancies conceived soon after stopping oral contraceptives is unknown. It is recommended that for any patient who has missed two consecutive periods, pregnancy should be ruled out before continuing the contraceptive regimen. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at the time of the first missed period (or after 45 days from the last menstrual period if the progestogen-only oral contraceptives are used), and further use of oral contraceptives should be withheld until pregnancy has been ruled out. If pregnancy is confirmed, the patient should be apprised of the potential risks to the fetus and the advisability of continuation of the pregnancy should be discussed in the light of these risks. It is also recommended that women who discontinue oral contraceptives with the intent of becoming pregnant use an alternate form of contraception for a period of time before attempting to conceive. Many clinicians recommend three months although no precise information is available on which to base this recommendation. The administration of progestogen-only or progestogen-estrogen combinations to induce withdrawal bleeding should not be used as a test of pregnancy. 6. GALLBLADDER DISEASE. Studies report an increased risk of surgically confirmed gallbladder disease in users of oral contraceptives and estrogens. In one study, an increased risk appeared after two years of use and doubled after four or five years of use. In one of the other studies, an increased risk was apparent between six and twelve months of use. 7. CARBOHYDRATE AND LIPID METABOLIC EFFECTS. A decrease in glucose tolerance has been observed in a significant percentage of patients on oral contraceptives. For this reason, prediabetic and diabetic patients should be carefully observed while receiving oral contraceptives. An increase in triglycerides and total phospholipids has been observed in patients receiving oral contraceptives. The clinical significance of this finding remains to be defined. 8. ELEVATED BLOOD PRESSURE. An increase in blood pressure has been reported in patients receiving oral contraceptives. In some women hypertension may occur within a few months of beginning oral contraceptive use. In the first year of use, the prevalence of women with hypertension is low in users and may be no higher than that of a comparable group of nonusers. The prevalence in users increases, however, with longer exposure, and in the fifth year of use is two and a half to three times the reported prevalence in the first year. Age is also strongly correlated with the development of hypertension in oral contraceptive users. Women who previously have had hypertension during pregnancy may be more likely to develop elevation of blood pressure when given oral contraceptives. Hypertension that develops as a result of taking oral contraceptives usually returns to normal after discontinuing the drug. 9. HEADACHE. The onset or exacerbation of migraine or development of headache of a new pattern which is recurrent, persistent, or severe, requires discontinuation of oral contraceptives and evaluation of the cause. 10. BLEEDING IRREGULARITIES. Breakthrough bleeding, spotting, and amenorrhea are frequent reasons for patients discontinuing oral contraceptives. In breakthrough bleeding, as in all cases of irregular bleeding from the vagina, nonfunctional causes should be borne in mind. In undiagnosed persistent or recurrent abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy. If pathology has been excluded, time or a change to another formulation may solve the problem. Changing to an oral contraceptive with a higher estrogen content, while potentially useful in minimizing menstrual irregularity, should be done only if necessary since this may increase the risk of thromboembolic disease. Women with a past history of oligomenorrhea or secondary amenorrhea or young women without regular cycles may have a tendency to remain anovulatory or to become amenorrheic after discontinuation of oral contraceptives. Women with these preexisting problems should be advised of this possibility and encouraged to use other contraceptive methods. Postuse anovulation, possibly prolonged, may also occur in women without previous irregularities. 11. ECTOPIC PREGNANCY. Ectopic as well as intrauterine pregnancy may occur in contraceptive failures. 12. BREAST FEEDING. Oral contraceptives given in the postpartum period may interfere with lactation. There may be a decrease in the quantity and quality of the breast milk. Furthermore, a small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs. The effects, if any, on the breast-fed child have not been determined. If feasible, the use of oral contraceptives should be deferred until the infant has been weaned. **PRECAUTIONS: General:** 1. A complete medical and family history should be taken prior to the initiation of oral contraceptives. The pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen and pelvic organs, including Papanicolaou smear and relevant laboratory tests. As a general rule, oral contraceptives should not be prescribed for longer than one year without another physical examination being performed. 2. Under the influence of estrogen-progestogen preparations, preexisting uterine leiomyomata may increase in size. 3. Patients with a history of psychic depression should be carefully observed and the drug discontinued if depression recurs to a serious degree. Patients becoming significantly depressed while taking oral contraceptives should stop the medication and use an alternate method of contraception in an attempt to determine whether the symptom is drug-related. 4. Oral contraceptives may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention, such as convulsive disorders, migraine syndrome, asthma, or cardiac or renal insufficiency. 5. Patients with a past history of jaundice during pregnancy have an increased risk of recurrence of jaundice while receiving oral contraceptive therapy. If jaundice develops in any patient receiving such drugs, the medication should be discontinued. 6. Steroid hormones may be poorly metabolized in patients with impaired liver function and should be administered with caution in such patients. 7. Oral contraceptive users may have disturbances in normal tryptophan metabolism which may result in a relative pyridoxine deficiency. The clinical significance of this is yet to be determined. 8. Serum folate levels may be depressed by oral contraceptive therapy. Since the pregnant woman is predisposed to the development of folate deficiency and the incidence of folate deficiency increases with increasing gestation, it is possible that if a woman becomes pregnant shortly after stopping oral contraceptives, she may have a greater chance of developing folate deficiency and complications attributed to this deficiency. 9. The pathologist should be advised of oral contraceptive therapy when relevant specimens are submitted. 10. Certain endocrine and liver function tests and blood components may be affected by estrogen-containing oral contraceptives: a. Increased sulfobromophthalein retention. b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability. c. Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered. d. Decreased pregnanediol excretion. e. Reduced response to metyrapone test. **INFORMATION FOR THE PATIENT: (See Patient Package Insert). DRUG INTERACTIONS:** Reduced efficacy and increased incidence of breakthrough bleeding have been associated with concomitant use of rifampin. A similar association has been suggested with barbiturates, phenylbutazone, phenytoin sodium, and ampicillin. **CARCINOGENESIS, PREGNANCY, NURSING MOTHERS: See CONTRAINDICATIONS and WARNINGS. ADVERSE REACTIONS:** An increased risk of the following serious adverse reactions has been associated with the use of oral contraceptives (see WARNINGS): Thrombophlebitis. Pulmonary embolism. Coronary thrombosis. Cerebral thrombosis. Cerebral hemorrhage. Hypertension. Gallbladder disease. Liver tumors. Congenital anomalies. There is evidence of an association between the following conditions and the use of oral contraceptives, although additional confirmatory studies are needed: Mesenteric thrombosis. Neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis. The following adverse reactions have been reported in patients receiving oral contraceptives and are believed to be drug-related: Nausea, usually the most common adverse reaction. Vomiting, occurs in approximately 10% or less of patients during the first cycle. Other reactions, as a general rule, are seen much less frequently or only occasionally. Gastrointestinal symptoms (such as abdominal cramps and bloating). Breakthrough bleeding. Spotting. Change in menstrual flow. Dysmenorrhea. Amenorrhea during and after treatment. Temporary infertility after discontinuance of treatment. Edema. Chloasma or melasma which may persist. Breast changes: tenderness, enlargement, and secretion. Change in weight (increase or decrease). Change in cervical erosion and cervical secretion. Possible diminution in lactation when given immediately postpartum. Cholestatic jaundice. Migraine. Increase in size of uterine leiomyomata. Rash (allergic). Mental depression. Reduced tolerance to carbohydrates. Vaginal candidiasis. Change in corneal curvature (steepening). Intolerance to contact lenses. The following adverse reactions have been reported in users of oral contraceptives, and the association has been neither confirmed nor refuted: Premenstrual-like syndrome. Cataracts. Changes in libido. Chorea. Changes in appetite. Cystitis-like syndrome. Headache. Nervousness. Dizziness. Hirsutism. Loss of scalp hair. Erythema multiforme. Erythema nodosum. Hemorrhagic eruption. Vaginitis. Porphyria. Impaired renal function. (ORTHO-NOVUM 1/50□21 and ORTHO-NOVUM 1/50□28 contain tartrazine. Allergic reactions have been reported with the ingestion of this dye in some patients.) **ACUTE OVERDOSE:** Serious ill effects have not been reported following acute ingestion of large doses of oral contraceptives by young children. Overdosage may cause nausea, and withdrawal bleeding may occur in females.

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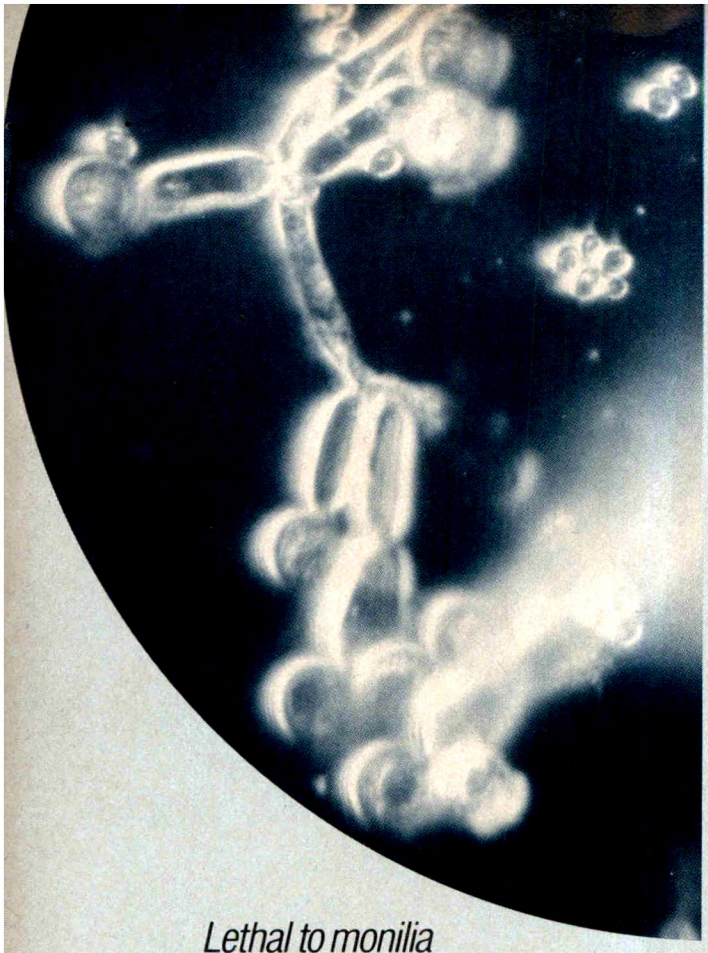
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1. Caraway, A.F.: Florida's Experience with an Intrauterine Device for the Nulliparous Patient. Presented at the International Family Planning Research Association Meeting, Palm Springs, California, October 21, 1974.
2. Caraway, A.F. and Vaughn, B.J.: J. Reprod. Med. *10*:170, April 1973.

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3. Hayes, O.J.: A Clinical Evaluation of the Intrauterine Device for Control of Conception. South. Med. J. *66*:254, Feb. 1973.
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7. Tietze, C.: Report of a New IUD: The Double Coil. Advances in Planned Parenthood, III:85, 1967.

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American Journal of Obstetrics and Gynecology

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Transactions of the Forty-sixth Annual Meeting of the Central Association of Obstetricians and Gynecologists

Time

Presidential address

WILLIAM B. GODDARD, M.D.
Lakewood, Colorado

THERE IS NO HIDDEN meaning in today's title, nor is it the acronym of some mysterious government agency or new form of health care. It is a discussion of the use and misuse of our professional time. It is an attempt to communicate to you the distillation of many discussions with friends, random thoughts during boring meetings, starts and false starts, broken New Year's resolutions, a few successes, and many failures. I suspect many of you will meet yourselves in the coming discussion.

A young man who graduated from medical school in my day had achieved much. He had been at or near the top of his class in high school and college and had gone through four years of training with men and women of similar achievements. He had mastered a great deal of cognitive knowledge and put in long, but productive hours. He knew how to study and more often than not was personable and had a wide range of interests. He then entered the internship for a one- to two-year period. He absorbed much knowledge in a short period of time, lived and breathed medicine, and spent long hours in the hospital. His course had many of the characteristics of a fugue.

He then moved on to residency and got more of the same. This was not necessarily at the demand of the senior staff, but frequently at the demand of his own desire for accomplishment. He frequently never left the hospital on the same calendar day as the one on which he entered. He was expected to tend the laboring mother all night, operate all morning, and solve problems in the clinic all afternoon. This pattern of life went on for three or four years. The resident emerged from these years superbly trained in obstetrics and gynecology, but he also had learned something else, and that was how it is to function when one is always tired. We train our residents to be tired. I submit that this is learned behavior, that many physicians never overcome this training, and this is an important reason that the physician's working habits are so markedly different from those of other people in our society. I do not think any of us need to look very far without thinking of people who have carried this habit the rest of their lives. This attitude, though less prominent in younger physicians, does not seem to have changed very much over the years. It is today enough of a problem that the Resident Physicians Section of the A. M. A. has found it necessary to set up a "Work Group on The Well-Being

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Reprint requests: Dr. William B. Goddard, 2020 Wadsworth Blvd., Suite 16, Lakewood, Colorado 80215.

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of Physicians in Training" and write, in their own words, "A Survivor's Manual."[1] Of course, we did voluntarily choose this training and none of us can plead that we were innocent when we entered it. I do not intend to discuss the so-called Type A personality and whether it is a fact or fiction, but I submit that we come out of our training program into practice feeling that most of our waking hours will be spent with medicine.

This habit is also seen in other professions, such as law and accounting, but is epitomized in medicine. The academician, too, is forever in trouble with time, though many university academic departments are wiser than we are; their departmental chairmanships are rotated, are frequently fobbed off on one of the newer members, and are not considered an honor. I have for years felt that the Chairmanship of a Department of Obstetrics and Gynecology is in many ways equivalent to being ridden out of town on a rail. It is the honor of the thing that makes up for the discomfort.

Time also is a problem in business and if you have ever found yourself on a businessman's mailing list, you will know that brochures for sessions on "The Management of Time", "Delegation of Authority", "Management by Objective," and similar titles are subjects of many symposia. As an aside, if you physicians think the cost of postgraduate medical education is high, you should see the tuition for these symposia.

So lack of time is a universal problem. We are all somewhat like the white rabbit of Lewis Carroll: "I'm late, I'm late, I'm late, for a very important date."

Let us look around us—and that includes in the mirror—how do doctors use their professional or working time? I am impressed that we do not use our time at all. Others use our time for us. We go in the morning to the operating room. We go at 7:30 for no sensible reason other than that nurses' morning shifts begin at 7:00 and it takes a half hour to get ready. We begin not when we wish to begin, but when the nurses wish us to begin. We may wait inordinate amounts of time between operations, and when we go on rounds we find that our patients are missing due to the requirements of x-rays, laboratory, and other hospital schedules. But then we do not schedule rounds at a predictable time, so we cannot complain. We go to the office where, to quote a well-known private practice analyst, "fifty percent of our practice is run by the patients, thirty-five percent by the office help, and fifteen percent by the physician."

One of our patients' major complaints is we do not schedule their appointments with any consideration for their time. We complain that we see too many patients, but how many of us, when a patient complains that she is unable to get an appointment, squeeze her in rather than compliment our receptionist on keeping to our agreed schedule. Soon our receptionist learns that we really like to be overscheduled. I submit that this attitude is a direct carryover from our residency days and one that we should be able to cure.

Many practicing physicians consider the telephone a monster rather than a quick and reliable means of communication. A query of these doctors reveals that they have never learned to set up guidelines for their receptionists to facilitate communication. It takes only a moment between patients to approve a plan of action with your nurse and a long time if you try to do it yourself. This, and I speak from experience, can be done very smoothly. In one hospital where I work, pagers are carried into the operating room. I for one have no interest in knowing in the middle of a hysterectomy that Mrs. Smith wishes her birth control prescription refilled before lunch.

The last major category of professional time is Committees and Meetings. You may not know it, but the true contents of Pandora's box was very probably a printing press and a committee meeting agenda.

John Galbraith, in *The New Industrial State*,[2] discussed committees pointed out that power once transferred to the committee could not be retrieved, and discussed the effect of this fact on decision making. However, he discussed another type of committee. He called these ceremonial or representational committees and felt that they were useful to give apparent representation to various groups within power structures, but had no real input into the decision-making process. Do you see yourself there? I serve on far fewer committees since recognizing this fact and I would like to suggest to you that you look at the committee meetings you attend, divide them into the two functional groups—decision-making and ceremonial—attend the first and ignore the second. Do this for a year and then look back; you will note that the world is unchanged

Another time waster, supposedly needed for good medical care, is the hospital meeting. Does anyone, including the Joint Commission on Accreditation, really believe that these hours of jumping from subject to subject, and self-serving audit to self-serving audit, really improve the care of the patient? If they do not, why do we continue to go? An integrated postgraduate course on a single subject, or a meeting such as this one, is more likely to improve your care of the patient. Useless meetings are a major problem in our profession.

A largely unrecognized time problem in our profession is the medical record. In one of the buildings of the Mayo Clinic there used to be a glass case and in that case was a large, solid, bound book, the first case-book

of the Mayo Clinic. In that book appeared page after page of patient visits. Each visit was headed by the patient's name, and in the front of the book was a list of patients arranged alphabetically, and after each patient's name was recorded the number of each page on which a visit by that patient appeared. In reading those I was impressed: first, the penmanship was much better; second, the grammar was much better; third, the observations were more carefully made; fourth, the only change in recording of medical data since that time has been to put those patient visits on individual sheets of paper and file them in a manila folder. The narrative record is unchanged.

The recently popular problem-oriented chart may be an improvement in the proper hands, but on many charts, the beloved "SOAP" consists of substituting subjective for history, objective for physical, assessment for diagnosis, and plans for treatment, without real change in content or organization.

I would like to suggest that the best medical charts in the world are the obstetric charts. They are time-oriented, they are tabular, and many parameters are graphed rather than written. The flow and direction of the patient's condition are obvious at a glance, and deviations from normal are quickly spotted. This chart organization gives a clarity comparable to the temperature chart. Can we not in some manner apply this notion to the gynecologic chart and, indeed, to all medical charts? There are some physicians who, at least in their offices, have applied this to their own charting and it gives much more clarity and much more accuracy to their management. We should begin to push the expansion of this idea into the hospitals.

You may say, "So what!" If the social anthropologists are correct, we do not think abstractly, we think in a language, and our charts are the language of medicine.

Mathematics has developed only as the mathemetician has been able to manipulate agreed-upon symbols and the same development is true of physics and chemistry. The symbolic logic of George Boole has become the basis of the entire world of the computer.

I would suggest that medicine can progress rapidly only in the areas in which we abandon the narrative form, develop agreed-upon symbols to represent our basic information about the patient, and then learn to manipulate those symbols in a mathematical manner. The mathematics is already available, and has been available since the nineteenth century, in the form of Bayes' Theorem and other formulas, but the data on which to operate have not been available. This lack of data is primarily because of our primitive method of record keeping and the habits of thought engendered by that record keeping.

For simple examples of what I am talking about, I refer you to *Surgical Decision Making*, by Eiseman and Wotkyns,[3] and to Chapter 17 of *Costs, Risks and Benefits of Surgery*.[4] Most of us do not have twenty years of experience in medicine. We have one year's experience repeated twenty times. The purpose today is not to inflict upon you a radical medical record, but to get you thinking that our present record is primitive and needs improvement. We think the way we write, not the other way around, and the medical record has been an impediment to clear medical thinking.

If time is a problem, how are we to obtain time? Different things work for different people. Almost every person I have known who accomplishes a great deal, whether it be in medicine or in cultivating roses, does it in the morning. There are no interruptions; the phone does not ring. There are no hospital committee meetings, the children are not up—nor, for that matter, is the sun.

You may say, "I used to be able to do it, but I cannot any more." I am indebted to Prof. John Beazley for the following practical hint: set your alarm clock five minutes early. It is too short a time to go back to sleep and you can make a cup of coffee. After several days, add five more minutes, and so on until you have an hour or more. This is a recent experiment which appears to be bearing fruit.

Another suggestion, which is not yet bearing much fruit, is to structure your time. This seems to be the most difficult discipline of all for physicians. The telephone intrudes, we add that extra patient, the previous surgeon goes over his scheduled time in the operating room, meetings run overtime, and on and on. Have your secretary call you 55 minutes into every committee meeting with a carefully scheduled emergency call. It is interesting how this speeds up agendas and assists in the structuring of your time.

Another suggestion is the retreat. Its increasing popularity in business and hospital planning sessions is evidence of its usefulness. Its advantages are total absence of the daily routine of office and family, concentration on the subject at hand, and interaction with others of similar interests. But does a retreat need to be a group session? Do you remember studying for your Boards? Do you remember writing a paper? Do you remember that one's efficiency seemed to be greatest then, with the pressure of time at your back and a clearly defined goal? Have you considered a similar approach to reading the medical literature, rereading Shakespeare's plays, or, for that matter, learning to program a computer? The concept of the retreat is worthwhile even though you are the only one retreating.

Another suggestion is to delegate authority. We physicians are egoists and compulsives and we have difficulty with consistent delegation of authority. It is this ability to delegate that separates the truly good administrator from others. It is an ability that appears to be almost wholly lacking in physicians, particularly those in private practice. It is said that behind every great man stands a good executive secretary, and a look at the salaries of executive secretaries in corporations should convince you of the truth of this statement. Conscious and consistent delegation of authority can be learned. It is in this area that the practice management consultant gives his message, a message frequently ignored.

A major opportunity for the physician to improve his use of time is through the use of computers. Please note that I am suggesting the use of the computer as a means of changing our way of thought, i.e., as a process rather than an end in itself. This notion is quite different from the usual use of computers today.

We are all aware of the cute phrases, such as "garbage in, garbage out," "IBM stands for "I've been moved;" and "a computer can make more mistakes in 20 seconds than 20 men working 20 years." These phrases do have a ring of truth to them, but something new and spectacular, and as yet dimly recognized, is happening in the computer field. Until the last three years, the computer has been a big device, growing ever bigger, requiring air-conditioned rooms, mahouts who tend it from birth to retirement, and a large supply of kilobucks. Many physicians who have tried to use computers have been turned off due to their complexity and the professional programmer's attitude of Procrustes; he cuts you to fit his programs.

But something has happened. In about 1975, due to the plummeting cost of integrated circuitry, the microcomputer developed; progress has been rapid since. Look back to 1961 when IBM introduced the 360 Series Computer. You can buy, today, a computer with the power equal to the largest pre-1961 machine for about $3,500. If you wish to add all of the bells and whistles, and a good printer, you will have a tough time spending more than $6,000. You can have a computer, which fits on your desk, more powerful than any computer made before 1961, for less than the price of a new car.

Is this too good to be true? What are the problems? It is slow, and when it comes to getting it to do what you want it to do, there is as yet no programming help out there whatsoever. The cliché that the computer does what you told it to do and not what you thought you told it to do, has never been closer to the truth. However, new languages are rapidly developing which will allow you to talk to the stupid things in comfortable, English phrases, and programming the computer yourself is becoming easier.

The most common computer language at present is BASIC, but BASIC is twenty years old and new languages, such as Pascal, and a medically oriented one with the delightful acronym of MUMPS, are becoming popular for the nonprofessional user.

There are many people standing behind airline and hotel reservation counters who do not think computers are hard to use. Why not doctors? The breakthroughs in computer price and languages are giving us an opportunity to change our modes of thought and structure our knowledge.

A final problem in our use of time is the divided nature of our specialty.

For many years, we have been trained as obstetricians and gynecologists and it has been felt, and properly so, that a specialist must know the female in both her pregnant and her nonpregnant state. When it comes to practice, we have a double specialty, with obstetric practice patterns quite different from gynecologic practice patterns. In the days when I practiced both sides of the specialty, I recognized a constant need for changing of my mental gears from day to day and minute to minute and over the years it became increasingly frustrating.

The historical thrust of medicine has been toward greater and greater specialization, not less and less, and I must question the virtues of the continued practice by one individual of the double specialty. The old eye, ear, nose, and throat physician has disappeared; "ear, nose, and throat" is separating into ear on the one hand and nose and throat on the other, and no one is mourning the passing. The general internist is disappearing into the specialty of family practice and is being replaced by the cardiologist, the gastroenterologist, the pulmonary specialist, the endocrinologist, the allergist, the specialist in diabetes, and the specialist in arthritis. This is reckoned as progress and probably is.

In our specialty, we have the identifiable subspecialties of reproductive endocrinology, oncology, and maternal-fetal medicine, and we, too, reckon this as progress. Can we logically cling to the notion that we are obstetricians and gynecologists and are we surgeons or primary-care physicians? With that sentence I plead guilty to having fallen into a semantic trap, only recently recognized. Primary-care physicians and surgical specialists are not opposite sides of the same coin. Recently, our secretary has been appointed a Governor of the American College of Surgeons. In our spring *Newsletter,* he encouraged our members, as surgical specialists, to apply also for membership in that organization.

For these efforts he received a critical letter from the Director of The American College of Surgeons saying, and I quote, "The official position of obstetrics-gynecology at the present time is that they represent a primary-care specialty, and as such, it appears anomalous to categorize them as a surgical specialty." Further on "Obstetrics/gynecology is widely thought of as a non-surgical discipline."[5] The semantic trap is the notion that surgical care is episodic and that long-term periodic evaluation of an individual's problems (primary care) is somehow "unsurgical" and, therefore, to be condemned.

Stay out of the trap of believing first, that primary care and surgical specialization are mutually exclusive, and second, that periodic evaluation is somehow demeaning to the surgeon and that episodic care is not.

Is it not time to consider separating *at the practice level* obstetrics from gynecology? Obstetrics is a 24 hour, quasiemergency form of medicine, with the proper prenatal evaluation of the mother and fetus becoming an increasingly important and increasingly complicated activity. Much of it requires the presence in the hospital of both patient and physician. Delivery is becoming simpler. It is a pity, but manipulative obstetrics is rapidly becoming a lost art, and it appears that an increasingly common indication for cesarean section is "threatened spontaneous delivery." Whether the exploding levels of cesarean-section deliveries are the wave of the future, or a temporary aberration, only the future will tell, but certainly, obstetrics is more complicated, more time consuming, and more demanding of the physician than it used to be in the days of general anesthesia and "perineal obstetrics."

On the other hand, gynecology also is becoming more complicated, despite the belief of some that all we can do is hysterectomies. Most evaluations of gynecologic-endocrine problems are still done by the ordinary practicing gynecologist. Most malignancy is still treated by him and the clinical acumen required for the use of estrogen and the birth control pills is certainly not decreasing. Our surgery is changing; the colposcope, the laparoscope, and the operating microscope are developing in our specialty a whole class of what I choose to call "instrument-dependent" surgical procedures. Most gynecologic practice is of a scheduled, structured type and most of our surgery is planned and elective as opposed to urgent and emergent.

Thus it appears that the modern obstetrician-gynecologist is on the horns of a dilemma. Each half of his double specialty requires different work patterns and, most importantly, different habits of thought. It is any wonder that many are frustrated? This is not advocacy of return to the old Johns Hopkins type of complete separation, but the formal recognition within the field of obstetrics/gynecology of the already existing differences in interests of men within our own specialty. Why advocate this? I would be terribly unhappy if you interpret this as an attempt to destroy our cohesiveness, for rather it is an attempt to strengthen our double specialty. Obstetrics/gynecology has recognized the need for recognition of special-interest groups within the specialty by the formation of the three presently approved subspecialty groups. We need to add at least one more: gynecologic surgery. We may need to add others in the future. It may be good that we have been rebuffed by the American College of Surgeons, for this may stimulate expanded recognition of special interest groups within the traditional organization of our specialty, for only in this way will obstetrics/gynecology continue to grow.

This has been a somewhat personal talk, but all experience is personal and if some of you agree with these ideas and are encouraged to try them, or if you disagree and are encouraged to prove me wrong, then the talk will have been worthwhile.

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Prolactin-secreting pituitary adenomas in women

II. Menstrual function, pituitary reserves, and prolactin production following microsurgical removal

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A prospective study of 46 women with prolactin-secreting pituitary adenomas and amenorrhea and/or galactorrhea was performed to determine the influence of the selective transsphenoidal removal of these tumors on pituitary and reproductive function. This procedure was effective in restoring menstrual function in 34 of 41 women and in eliminating lactation in 30 of 40 women. Tumor size and preoperative serum prolactin concentrations were the most important factors in predicting the postoperative disappearance of symptoms. Normal menstrual function returned in 33 of 34 women with tumors <2 cm in diameter but in only one of seven women with tumors >2 cm. Similarly, galactorrhea disappeared in 29 of 34 women with tumors <2 cm but in only one of six women with larger tumors. Menses returned in 31 of 32 women and galactorrhea disappeared in 25 of 31 women with preoperative serum prolactin levels below 200 ng/ml; conversely, menses returned in only three of nine women and lactation ceased in one of six women with preoperative serum prolactin concentrations above 200 ng/ml. Prolactin concentrations decreased in 42 of 43 patients following the removal of pituitary adenomas and returned to normal in 30. Postoperative pituitary reserves of adrenocorticotropic hormone, growth hormone, luteinizing hormone, and follicle-stimulating hormone were normal in most patients. These data indicate that the removal of prolactin-secreting pituitary adenomas by a neurosurgeon accomplished in this surgical technique is effective in restoring menstrual function and eliminating lactation in most women, especially if the tumor is <2 cm in diameter and the preoperative serum prolactin concentration is <200 ng/ml.
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PRIOR TO 1974, reports of the neurosurgical removal of pituitary adenomas in women with amenorrhea or galactorrhea described a discouraging incidence of operative complications and postoperative pituitary dysfunction. These results were due in part to the surgical techniques and in part to the destruction of normal pituitary tissue by relatively large tumors. Since 1974, there have been several reports of the selective microsurgical removal of small prolactin-secreting adenomas (microadenomas) with infrequent complications and preservation of normal pituitary function.[1-7] However, factors that influence the postoperative pituitary and reproductive function of women with prolactin-secreting adenomas have not been elucidated in these reports.

Therefore, we studied the influence of the duration of amenorrhea and galactorrhea, age at the time of

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surgery, preoperative and postoperative prolactin serum concentrations, and tumor size on the resumption of menses and disappearance of galactorrhea following the transsphenoidal removal of prolactin-secreting adenomas. In addition, we determined the postoperative reserves of pituitary trophic hormones and quantitated serum prolactin concentrations during the first 12 months postoperatively.

Material and methods

Clinical material. Forty-six women, aged 15 to 50, with histologically proved prolactin-secreting pituitary adenomas were studied. These women presented with primary amenorrhea, secondary amenorrhea of at least 6 months' duration, and/or galactorrhea. The presumptive diagnosis of a pituitary adenoma was made on the basis of an elevated serum prolactin level and an abnormal hypocycloidal polytomogram. A detailed review of the historical data and physical features of 25 of these patients has been reported previously.[7]

Each patient was evaluated by at least one of the authors prior to surgery and at 3 to 6 month intervals following surgery.

Treatment. Transsphenoidal microsurgical exploration of the sella was performed on all 46 patients. Adenomas were identified and selectively removed in toto when possible. In addition, the tumor site was curetted and treated with absolute alcohol. Three patients in whom removal of the adenoma was judged incomplete at the time of operation received postoperative irradiation.

Endocrine evaluation. Baseline serum concentrations of luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactin, thyroid-stimulating hormone (TSH), cortisol, and growth hormone (GH) were obtained preoperatively and on at least one occasion at 3, 6, or 12 months postoperatively. In addition, anterior pituitary trophic hormone reserves were determined for LH, FSH, adrenocorticotropic hormone (ACTH), and GH prior to surgery and at 3, 6, or 12 months postoperatively. To assess LH and FSH reserves, gonadotropin-releasing hormone* (GnRH) was administered as an intravenous bolus of 100 μg at t = 0. GnRH was administered in the early follicular phase in women who were menstruating. Blood samples were obtained through an indwelling catheter at t = −30, −15, 0, +5, +10, +15, +20, +25, +30, +45, +60, +90, and +120 minutes and assayed for LH and FSH. To assess GH and ACTH reserves, insulin tolerance tests were performed with crystalline insulin (0.1 U/kilogram of body weight), administered as an intravenous bolus at t = 0. Blood samples were obtained through an indwelling catheter at t = −10, 0, +15, +30, +45, and +60 minutes and assayed for GH, cortisol, and glucose. An increase of 5 ng/milliliter or more of growth hormone and an increase of 8 μg/milliliter or more of cortisol were considered normal.

Assay procedures. Serum LH and FSH were measured by radioimmunoassay as previously described.[8] Results are expressed as equivalents of the Second International Reference Preparation of Human Menopausal Gonadotropin in milli–International Units (mIU) per milliliter of serum. Serum prolactin concentrations were measured by a homologous radioimmunoassay and are expressed as nanograms of human prolactin (VLS No. 3 standard) per milliliter of serum.[9] Immunoreactive human GH was assayed according to the modified method of Grodsky and Forsham.[10] Plasma cortisol was determined by a fluorometric method.[11]

Results

Postoperative reproductive function. Menses returned in 34 of the 41 patients (83%) with preoperative amenorrhea who were observed from 3 months to 3 years postoperatively. Seven women have not resumed menses after surgery. No menstrual information is available in three patients who were lost to follow-up following their initial postoperative examination. Two women had preoperative amenorrhea because of a previous hysterectomy, one of whom also had ovarian failure.

Lactation has disappeared in 30 of the 40 patients (75%) with preoperative galactorrhea who have been observed from 3 months to 3 years postoperatively. Two patients did not have galactorrhea prior to surgery and no current information is available on four patients.

Relation to age. When patients were placed in order according to age, a difference in postoperative return of menses was observed between women less than 30 years of age and those more than 30 years of age at the time of surgery (Table I). This difference was, however, not statistically significant. The return of menses was more frequent in women less than 30 years of age at the time of surgery (24 of 26 or 92%) than in women over the age of 30 (10 of 15 or 67%). However, four of the five women over 30 years of age with persistent amenorrhea had tumors larger than 2 cm in diameter, three of whom were judged to have subtotal removal of tumor. In addition, the two patients with persistent amenorrhea who were under 30 years of age at the time of surgery also had tumors greater than 2 cm in diameter.

There was no apparent relation between the postop-

*Supplied by S. Preston, M.D., Parke, Davis & Co., Detroit, Michigan.

Table I. Return of menses following surgical removal of a prolactin-secreting adenoma

	Total No. of patients	Return of menses	
		No.	%
Age (yr.):			
<30	26	24	92
>30	15	10	67
Duration of amenorrhea (yr.):			
<2	11	11	100
2-5	15	13	87
5-10	9	7	78
>10	6	3	50
Preoperative prolactin level (ng/ml):			
21-50	11	10	91
51-100	9	9	100
100-200	12	12	100
>200	9	3	33
Postoperative prolactin (ng/ml):			
<20	23	22	97
21-50	8	8	100
>50	8	3	37
Tumor size (cm):			
<1	18	18	100
1.1-2	16	15	94
>2	7	1	14

erative cessation of galactorrhea and age at the time of surgery. There was no evidence of spontaneous galactorrhea following surgery in 12 of 16 patients (75%) who were 30 years of age or older at the time of surgery. Spontaneous galactorrhea was absent postoperatively in 18 of 24 women (75%) who were under the age of 30 at the time of surgery.

Relation to duration of amenorrhea. When patients were ranked according to the duration of amenorrhea, there appeared to be a slight difference between those with greater than and those with less than 5 years of amenorrhea (Table I). Menses returned following surgery in 10 of 15 (67%) women who had amenorrhea for 5 years or more prior to surgery and in 24 of 26 (92%) women who had less than 5 years of amenorrhea. However, four of the five patients with persistent postoperative amenorrhea who had greater than 5 years of amenorrhea also had tumors greater than 2 cm in diameter. Similarly, both patients with persistent amenorrhea who had less than 5 years of preoperative amenorrhea had tumors greater than 2 cm in diameter. There did not appear to be a relation between the duration of preoperative galactorrhea and the cessation of lactation following surgery. Galactorrhea disappeared in 11 of 14 (79%) women with galactorrhea for 5 years or more and 19 of 26 (73%) of those with galactorrhea for less than 5 years.

Relation to prolactin concentration. Menses resumed in 31 of 32 (97%) women (Table I) with preoperative serum prolactin concentrations less than 200 ng/ml compared to three of nine with prolactin concentrations greater than 200 ng/ml ($p < 0.05$). However, menses returned significantly more often (31 of 32 or 97%) in women with preoperative serum prolactin concentrations less than 200 ng/ml ($p < 0.05$). Postoperatively, lactation disappeared in five of nine (56%) with preoperative prolactin concentrations greater than 200 ng/ml and in 25 of 31 (80%) with prolactin concentrations less than 200 ng/ml. The return of menses and cessation of galactorrhea were also related to the postoperative prolactin concentrations, as menses returned in only three of eight (38%) with postoperative prolactin concentrations greater than 50 ng/ml, while menses returned in 30 of 31 (97%) with prolactin concentrations 50 ng or less ($p < 0.05$) (Table I). Similarly, galactorrhea occurred in four of eight 50%) with postoperative prolactin concentrations greater than 50 ng/ml and 26 of 30 (87%) with prolactin concentrations less than 50 ng/ml. Postoperative prolactin concentrations or complete postoperative clinical data were not available for eight patients.

Relation to size of adenoma. As noted above, tumor size at the time of surgery was the factor most closely related to postoperative return of menses or disappearance of lactation (Table I). Only one of seven patients (14%) with a tumor 2 cm or greater in diameter as compared to 33 of 34 (97%) with tumors less than 2 cm in diameter had a postoperative return of menses ($p < 0.005$). Similarly, one of six women (17%) with tumors 2 cm or greater and 29 of 34 (85%) with tumors less than 2 cm had postoperative disappearance of lac-

tation. Information was incomplete regarding lactation following surgery in six patients.

Postoperative prolactin concentrations. The serum prolactin concentration was determined within the first 3 months following surgery in 43 patients. In 42 patients, the postoperative prolactin concentration was lower than prior to surgery (66 ± 7 versus 234 ± 97 ng/ml). The prolactin concentration did not change in the remaining patient. Postoperative serum prolactin concentrations were normal (<20 ng/ml) in 28 women and elevated in 15 in the first 3 months following surgery.

In addition, serum prolactin concentrations were determined at 6 or 12 months following surgery in 25 patients, 14 of whom had normal prolactin concentrations at 3 months (Fig. 1). The serum prolactin concentration remained normal at 6 or 12 months in the 14 patients who had normal prolactin concentrations at 3 months following surgery. Serum prolactin levels continued to fall in four of the eight who had elevated levels at 3 months and who did not have postoperative pituitary irradiation with a return to normal in two patients. All three patients who had postoperative irradiation had a continued fall in prolactin concentration.

The fall of prolactin soon after surgery was paralleled by the rapid disappearance of amenorrhea in those who resumed menses following surgery. Detailed menstrual information, available in 30 of the 34 patients in whom menses resumed, indicated menstrual bleeding within the first 3 months in 22 patients, with five of these 22 noting menses within the first postoperative month. Menses returned 6 months or more following surgery in eight patients. The mean time to return of menses was 3.4 ± 0.8 months in these 30 women. All 10 women in whom menses resumed within the first 2 months following surgery had normal postoperative prolactin concentrations, whereas only 10 of 20 (50%) in whom menses resumed 3 months or more after surgery had normal prolactin concentrations within the first 3 months after surgery. Detailed information was available in 29 of the 30 patients who noted a cessation of lactation following surgery. Lactation had ceased in 17 patients by 3 months, in 27 patients by 6 months, and in 29 patients by 12 months. Postoperative prolactin concentrations were normal in 15 of the 17 who noted the disappearance of galactorrhea within the first 3 months but were normal in only seven of 12 who noted the disappearance of lactation 3 or more months following surgery.

Postoperative pituitary function. LH and FSH reserves were determined in 22 women in whom menses resumed and in five women who remained amenorrheic following surgery. LH responses to GnRH were similar to those seen in the early follicular phase of the menstrual cycle (maximal increase from baseline of 15 to 75 mIU/ml) in 17 of the 22 women in whom menses resumed postoperatively, and in three of five who remained amenorrheic. Responses were blunted in one woman in whom menses resumed and in two in whom menses did not resume. Responses similar to those seen in the late follicular phase (maximal increase from baseline greater than 100 mIU/ml) occurred in four women in whom menses resumed.

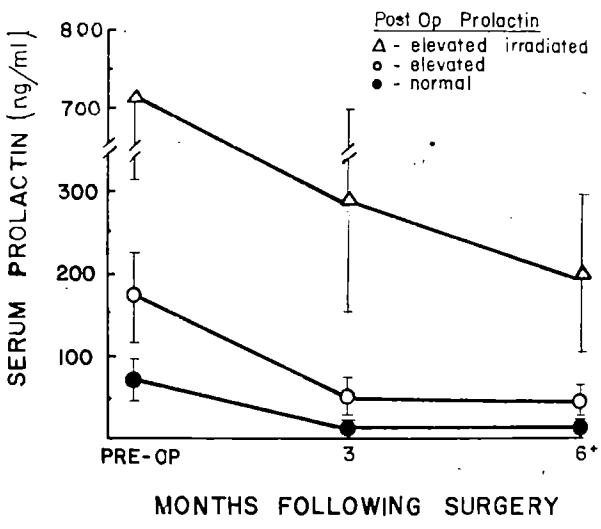


Fig. 1. Serum prolactin concentrations (mean ± SE) prior to and at 3 and 6 to 12 months following the removal of a prolactin-secreting pituitary adenoma in 25 women.

FSH levels rose in response to GnRH in all 27 women who were studied postoperatively, including the five women who remained amenorrheic. These responses were similar to those seen in the early follicular phase of the normal menstrual cycle. Postoperative GH and ACTH reserves were determined in 28 women. GH reserves, as reflected by an increase of ≥5 ng/ml, were normal in 20 of 24 women in whom menses resumed and in two of four who remained amenorrheic. Blunted or absent responses were present in the remaining six women. Pituitary ACTH reserves, as reflected by an increase of ≥8 μg/ml in the serum cortisol concentration, were normal in 22 of 24 women in whom menses resumed and four women who remained amenorrheic. Blunted responses were seen in two women, in both of whom menses returned.

Comment

This study confirms our preliminary report that suggested that the transsphenoidal removal of prolactin-secreting adenomas is effective in restoring menstrual function and eliminating lactation in most women with

these tumors.[7] In the present study, menses returned in 83% and lactation ceased in 75% of women following transsphenoidal surgery.

From the data presented here, tumor size and preoperative serum prolactin concentration appear to be the most important determinants in predicting postoperative disappearance of symptoms. Normal menstrual function returned in 33 of 34 women (97%) with tumors <2 cm in diameter but in only one of seven women (14%) with tumors >2 cm. Similarly, galactorrhea disappeared in 29 of 34 women (85%) with tumors <2 cm but in only one in six women (17%) with larger tumors. Menses returned in 31 of 32 women (97%) and galactorrhea disappeared in 25 of 31 women (80%) with preoperative serum prolactin levels below 200 ng/ml; conversely, menses returned in only three of nine women (33%) and lactation ceased in one of six women (17%) with preoperative serum prolactin concentrations above 200 ng/ml.

Consideration of certain clinical, radiologic, and endocrine observations assist in predicting which women have the greatest likelihood of normal reproductive function following surgery. A woman under the age of 30 with amenorrhea of less than 5 years' duration, who has a preoperative prolactin concentration of less than 200 ng/ml, a postoperative prolactin concentration of 50 ng/ml or less, and a tumor of less than 2 cm in diameter has greater than a 90% chance of resuming menses. Conversely, women over 30 years of age with long-standing amenorrhea, greatly elevated preoperative and postoperative prolactin levels, and large tumors have less likelihood that menses will resume. It is, therefore, important to screen young women with amenorrhea and/or galactorrhea of short duration for prolactin-secreting adenomas. At present such screening consists of measurement of the serum prolactin concentration followed by hypocycloidal polytomography of the pituitary sella in hyperprolactinemic women. The combination of hyperprolactinemia and an abnormal polytomogram has been found to be associated with a tumor over 90% of the time.[12]

If these adenomas are not the result of altered hypothalamic and/or neurotransmitter function, one would expect a return of normal pituitary endocrine dynamics and reproductive function following the selective removal of these tumors. Such a return of reproductive and pituitary function did occur in most patients when total removal of the adenoma was accomplished. While prolactin levels returned to normal in most women who had apparently complete removal of adenomas, prolactin levels remained persistently elevated in several following surgery. The persistent elevation in these patients may be due to the incomplete removal of the adenoma, the presence of an unsuspected second adenoma, a persistent abnormality in hypothalamic or neurotransmitter function, or hyperplasia of the lactotrophs which remained. The return of menses in almost all women who had complete removal of tumors and normal postoperative prolactin concentrations suggests that the hyperprolactinemia, per se, was causally related to the amenorrhea. It is unlikely that the amenorrhea was the result of a direct effect by the expanding mass of the tumor on the normal pituitary tissue, as many of the tumors were only a few millimeters in diameter, and there was very little distortion of the remaining gland with no decrease in gonadotropin reserves as determined by GnRH testing.

The selective removal of these tumors can be performed without gross disturbance of the function of the remaining pituitary gland as shown by the normal GH, ACTH, LH, and FSH reserves in most women in the postoperative period. Similar results have been reported recently by Jaquet and co-workers.[13] This demonstration of the integrity of the pituitary gland following surgery is important if one is to advocate the surgical approach to these tumors in patients whose only symptoms may be amenorrhea or galactorrhea.

In conclusion, the transsphenoidal selective removal of prolactin-secreting adenomas in women with amenorrhea or galactorrhea frequently can be accomplished with restoration of menstrual function provided that: (1) the tumor is relatively small (<2 cm in diameter), (2) the tumor is confined to the sella, and (3) the neurosurgeon is accomplished in this surgical technique. Surgery in these women almost always is followed by a return of prolactin levels to normal, the restoration of normal menses, and the disappearance of galactorrhea. Despite these encouraging findings, however, which patients should undergo such surgery remains to be established. The answer to this question awaits prospective studies comparing the long-term results of surgery, treatment with dopamine agonists such as bromergocriptine, or observation without treatment. Such a comparative study is currently in progress.

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Deformation and creep in the human chorioamniotic sac

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This paper presents a review of physical principles involved in deformation and creep in the human chorioamniotic membrane. These are definable rheological properties found in many materials. Experimental data are presented on 66 human fetal membranes. A difference in the stress tolerance between preterm and term membranes is demonstrated. A computer model has been devised which allows for the calculation of changes in thickness of the membrane at the point of fracture. This computer model allows for the study of the physical property of the tissue in ways which have not previously been suggested. The model suggests that the pathophysiology related to rupture of the membrane is based on changes in the thickness of this tissue occurring secondary to acute and chronic stress applications. The data derived in these experiments suggest a possible physical model for rupture of the membranes; they also introduce questions regarding the anatomic and biochemical makeup of the chorion and the amnion and the respective role that each plays in maintaining the integrity of the human chorioamniotic sac. (AM. J. OBSTET. GYNECOL. 134:366, 1979.)

RUPTURE OF THE chorioamniotic sac is a subject of critical concern in obstetrics.[1] The pathophysiology of membrane rupture remains a subject of speculation while the appropriate clinical approach is heatedly discussed.[2]

Different attempts have been made to assess the strength of the chorioamniotic sac and appreciate its particular properties. Reviews of such methodologies have been given by Danforth[3] and Artal[4] and their associates. The studies of Polishuk,[5] MacLaughlin,[6] and Parry-Jones[7] and their associates have contributed to our understanding of the physical nature of this tissue. The present research developed while the authors investigated the viscoelastic nature of human fetal membranes.[8]

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Sixty-five percent of fetal membranes normally rupture during the late first stage of labor.[9] However, a significant percentage rupture at inappropriate times. Premature rupture of membranes antecedes approximately one-third of all preterm deliveries. Various clinical conditions have been associated with premature rupture, but no unique physiologic or pathologic phenomenon has been consistently present with this clinical problem.

This paper investigates two specific aspects of the nature of human chorioamniotic membranes. First, an assessment is made of the stress tolerance in term and preterm membranes prior to experimental rupture. Second, the influence of recurrent stress application in reducing the thickness of membranes as devised by a computer model is studied. The results of this research implicate the importance of Braxton-Hicks contractions as a recurrent stress application in the fatigue of the membranes. Further, the normal physiologic growth process represents a chronic stress application in the over-all test of tolerance which the human chorioamniotic sac undergoes during pregnancy.

Theoretical concepts in the rheologic literature form the basis for the calculations subsequently described. These principles can be applied to biologic material. In the early 1940's Treloar[10] reported experimental results on the deformation of thin circular sheets of rub-

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ber (an elastic material) resulting from applied pressure. A theoretical description of the Treloar deflection profiles is given in a classical text by Green and Adkins.[11] The theoretical solutions rendered by Green and Adkins compared well with the experimental results of Treloar when elastic moduli for rubber proposed by Mooney[12] were used in the theoretical analysis.

Materials and method

The technique of applying pressure to fetal membrane samples in this research is conceptually similar to that used by Graham[13] in studying the elasticity of human skin. A description of the apparatus used in the research and the details concerning its construction have been published.[8] A sketch of the features of the apparatus is shown in Fig. 1. This apparatus was employed in a research thesis[14] which developed the procedure for determining elastic moduli of fetal membranes.

Membrane samples are obtained and processed within 1 hour of delivery. Specimens approximately 12 by 12 cm are mounted across a 7.62 cm opening in a Plexiglass mold. The membrane is positioned over a cylindrical chamber (shown in Fig. 1) so that the chorion interfaces with the liquid in the cylinder. The liquid medium filling this chamber is a pseudoamniotic fluid (PAF), developed by Schwartz and associates,[15] which is chemically and osmotically similar to human amniotic fluid. The amnion which is consistently facing upward is moistened with the same fluid. With the membrane samples mounted in place, pressure is recorded by a commercial physiograph.* The applied pressure range is 0 to 100 mm Hg. The fluid is removed from the lower chamber during a 30 second time interval, creating a deflection of the membrane downward. When a pressure of 10 mm Hg is obtained the exhaust valve is closed. An aluminum rod lying on the surface of the membrane descends with the evacuation of this fluid. The deflection of this rod is measured by means of a microscope mounted on a micrometer† slide with an accuracy of 0.005 mm. After the initial deflection, a waiting period of 3 minutes elapses. During this period, the pressure continuously decreases in an exponential manner. At the end of 3 minutes, the deflection of the rod is again measured. The exhaust valve is opened and the fluid is returned to the chamber, reducing the pressure again to zero. The membrane will rise back toward its original position. The time span for this pressure reduction is likewise 30 seconds. The rod deflection is again measured. The pattern is continued with fluid removal and deflection measurements obtained with the application of 20 mm Hg. Such cycles are continued with increments of 10 mm Hg until fracture occurs. During the experiments, the membrane is continuously observed and, at the time of rupture, the location of the fracture and its form is noted.

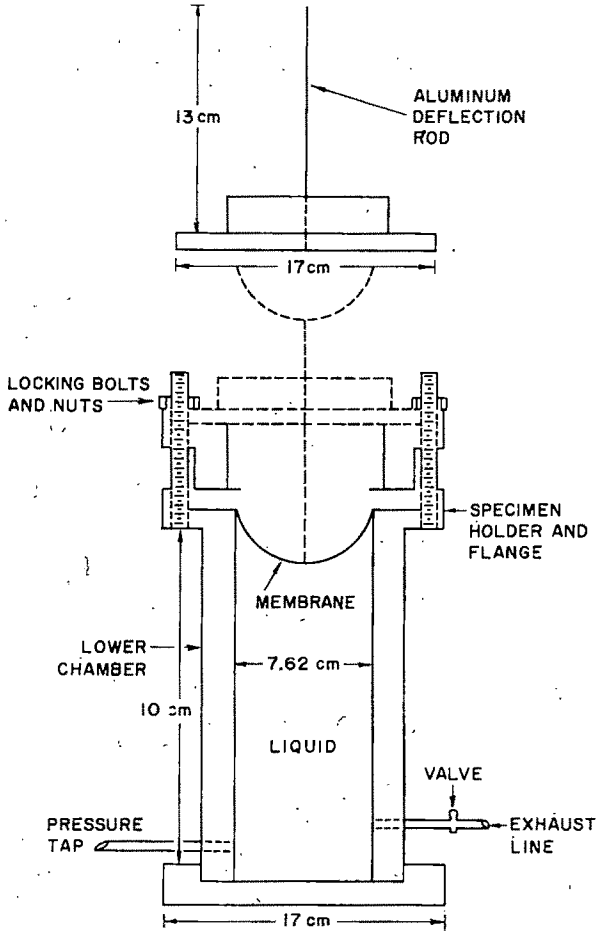


Fig. 1. Schematic diagram for membrane stress apparatus. Pressure tap extends to a transducer for recording on a physiograph.

In each cycle of experiments, the difference between the deflection reading at the end of the 3 minute cycle and the final reading when the pressure returns to zero is determined. This difference (W_0) is the pole deflection of the membrane due only to its elastic deformation. Creep (W_c) also develops in the material. This is represented by the difference between the W_0 reading and the initial reading at the beginning of the experiment.

Specimens of rubber 0.038 cm thick were placed in the apparatus. It has been shown[14] that rubber is an

*Narco Physiograph DMP-4B with Rectilinear Recorder Type 7070.

†Micrometer Slide Comparator, Gaertner Scientific Corp., Chicago, Ill.

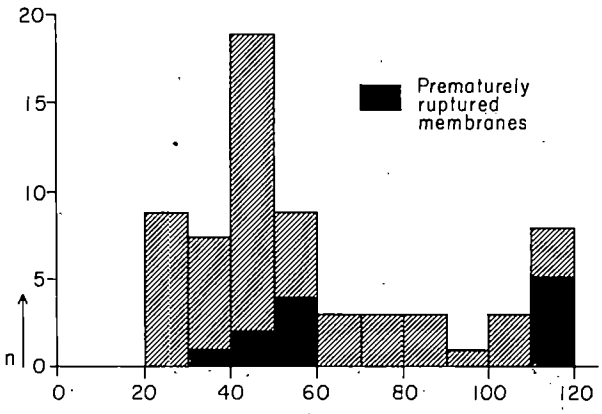


Fig. 2. P—Applied pressure at rupture (mm Hg).

elastic material, deformed in the same manner as fetal membranes. Since the elastic moduli for the rubber sample are well known, we were able to determine all of the kinematical quantities necessary to calculate extension ratios which are applicable to the fetal membranes when the deflection of the pole for fetal membranes is the same as rubber. Details for this methodology are discussed by Miller and Lavery.[16] In the present research the results of the rubber experiments present a calibration curve for determining the extension ratios once the pole deflections are measured for fetal membranes. These extension ratios are discussed subsequently.

The initial thickness of a membrane specimen in the undeformed state is measured prior to placing a part of it in the apparatus. A section of the membrane is placed between two Plexiglass plates. The membrane plate "sandwich" is placed on a flat surface. The micrometer slide comparator is placed proximate to the Plexiglass and the space between the glass loci is measured. Readings are taken between the inferior and the superior plate at five points. The average of these thicknesses constitutes the mean thickness of the membrane. This initial thickness is referred to as h_0. The thicknesses of membranes determined by means of this technique are similar to those found by other authors[4, 5] using different techniques.

In these experiments the data used in the calculations of physical properties include: pressure (P) affecting deformation of the membrane, the elastic deflection (W_0), the creep deflection (W_c), and the initial membrane thickness (h_0).

The computer program was written so that when the applied pressure (P), the maximum deflection at the pole (W_0), and the thickness of the membrane in the undeformed state (h_0) are known, then the stress distribution, the extension ratios, and the deflection profiles can be described. From this information, the

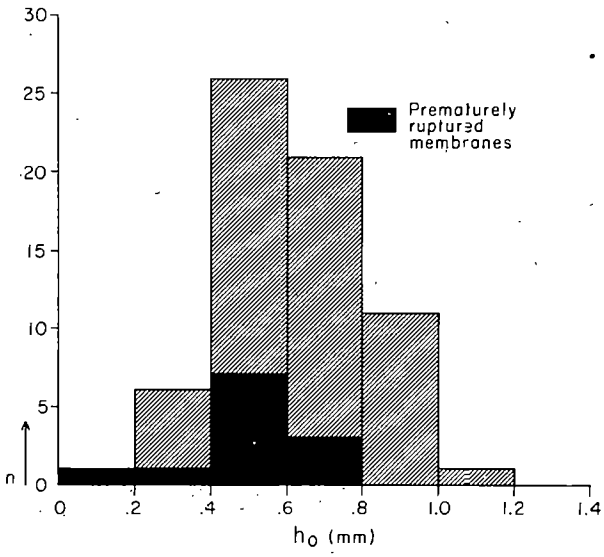


Fig. 3. Initial thickness (h_0) of membranes studied.

stress tolerance and changes in thickness during quasistatic testing have been calculated.

Results

Specimens of 66 deliveries were studied. Twelve (18%) were from gestations of less than 37 weeks.

The distribution of the maximum pressure needed to rupture the membrane is shown in Fig. 2. The results show that the rupture pressure for the largest population occurs at 40 mm Hg.

The distribution shown in Fig. 2 suggests a separate population of premature membranes which can tolerate pressures of a greater degree than normal term membranes. The shaded area in black represents the preterm part of that population. There was no apparent clinical background distinguishing these populations.

The distribution of the initial membrane thickness as measured by means of the method previously described is shown in Fig. 3.

The mean initial thickness for those membranes which rupture preterm spontaneously was 0.499 mm, for term membranes rupturing spontaneously was 0.545, and for those ruptured artificially at some point in labor was 0.643 mm.

The mean value for stress tolerance based on the rupture thickness was 124.2 kg/cm² (S.D. ± 126.3 kg/cm²) in the preterm group; for stress tolerance in term membranes rupturing spontaneously it was 49.59 kg/cm² (±69.96); for those term membranes which were ruptured artificially it was 49.61 kg/cm² (±55.32), as shown in Table I.

The difference between the stress tolerances of the preterm and term membranes was statistically sig-

Table I. Stress tolerance

	No. of cases	*Stress tolerance (kg/cm²)*	*S.D.*
Preterm*	12	124.2	±126
Term—spontaneous*	36	49.59	±70
Term—artificial	18	49.61	±55

*$p < 0.02$.

Table II. Membrane thickness at rupture (calculated)

	No. of cases	*Thickness (mm)*
Preterm*	12	0.097
Term—spontaneous*	36	0.155
Term—artificial	18	0.177

*$p < 0.03$.

nificant at the $p < 0.02$ level after an univarient analysis had been performed.

This suggested that preterm membranes can tolerate more stress application than term membranes.

The thickness at rupture for each membrane was calculated by Equation (4) (see immediately preceding Discussion). The mean value for the preterm membranes was 0.097 mm; for term membranes rupturing spontaneously it was 0.177 mm (shown in Table II). These populations were shown to be different at the $p < 0.03$ level after a univarient analysis had been performed. This suggests that the preterm membranes at the time of rupture become significantly thinner than their term counterparts.

In our research, the theoretical methods of Green and Adkins[11] were modified to determine deflection profiles, stress distributions, and extension ratio distributions over the entire surface of membranes tested. In making this modification one has to satisfy all the theoretical equations rendered by Green and Adkins[11] and at the same time develop deflection profiles which agree with actual experiments. The theoretical deflection profiles were compared to experimental results. They compare the expected deflection of rubber, the experimental finding of rubber, and the experimental finding of fetal membranes (shown in Fig. 4). The agreement is sufficient so that one is able to conclude that the extension ratios and the stress distributions are acceptable, especially in the range of $x = (r/a)$ from 0.2 to 0.5. This demonstration substantiates the subsequent principles employed in the mathematical model used to calculate stress tolerance and dynamic changes in thickness. The term r is the radial measure from the pole and a is the inner radius of the lower cylinder shown in Fig. 1. The elastic extension ratio distributions as a function of the radial distance from

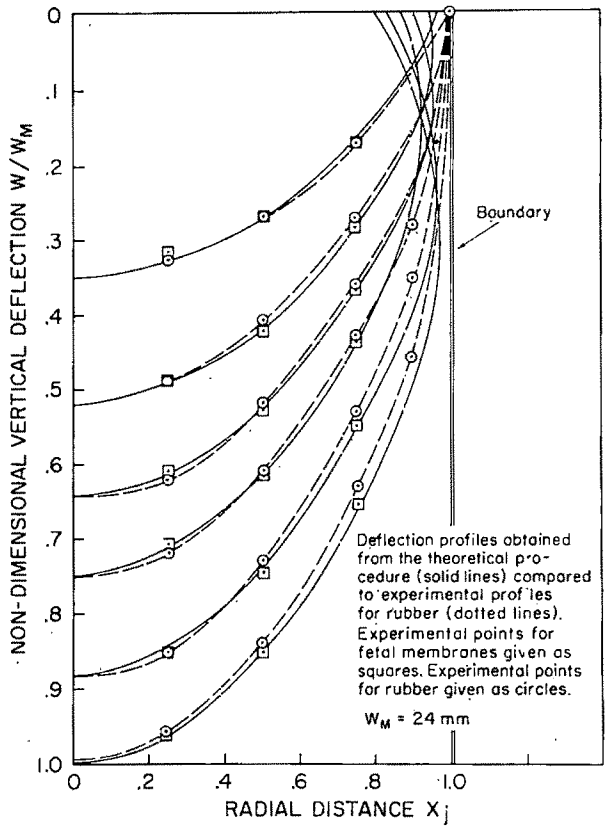


Fig. 4. Initial thickness of membranes prior to experimentation.

the pole are given in Fig. 5. There are three such relationships. One relationship (λ_1) describes extension ratios along longitudinal lines on the deformed membrane; a second relationship (λ_2) describes extension ratios along latitudinal lines on the deformed membrane; the extension ratio (λ_3) describes the change in thickness in a plane which transects the membrane in the deformed state. The curves shown in Fig. 5 are drawn for deflection $W_0 = 0.84$ cm produced by a pressure of 10 mm Hg in a representative specimen. The material whose deformation is described in Fig. 5 is a fetal membrane sample having an initial thickness of 0.380 mm. The stress distribution for the same membrane is given in Fig. 6. Only two curves are given in Fig. 6, since in the direction of λ_3 through the thickness of the membrane the stress is equal to zero. The curves such as shown in Fig. 5 and 6 can be produced for any fetal membrane whose elastic extension at the pole (W_0), the pressure producing the deflection (P), and the initial thickness (h_0) are known. These are the quantities which are measured in the present research. The elastic moduli and the stored elastic energy per unit volume can be calculated once the stress distribution and extension ratio distributions are known if one

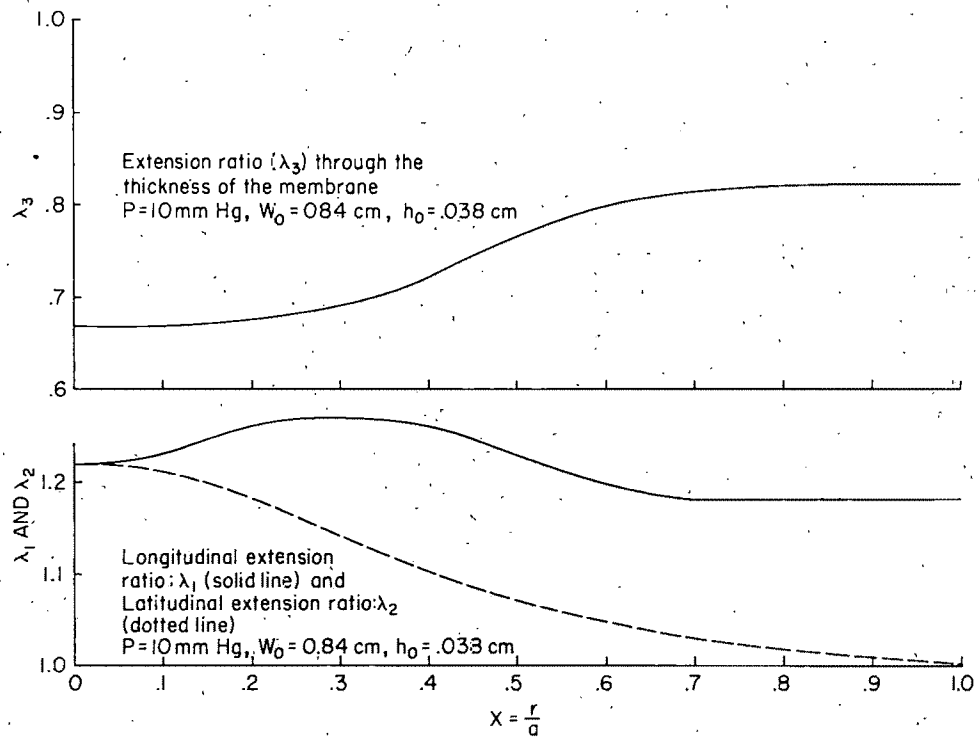


Fig. 5. Extension ratios.

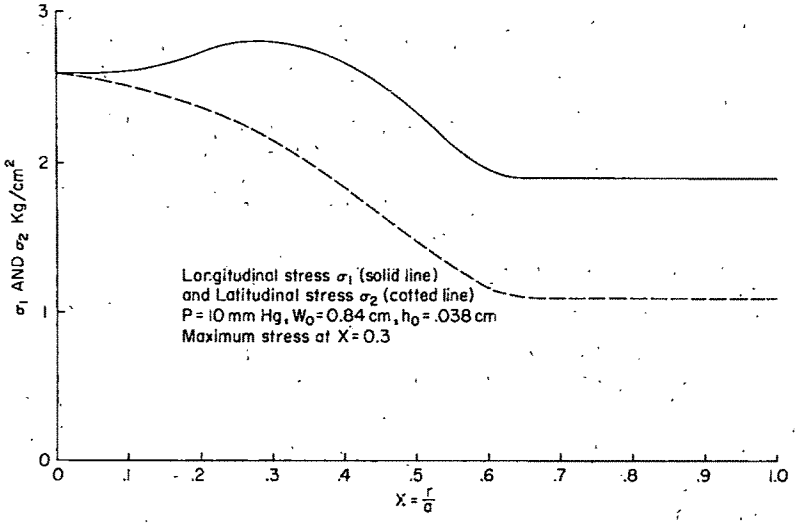


Fig. 6. Longitudinal and latitudinal stress.

assumes as for rubber that the elastic portion of fetal membranes is a Mooney material,[12] an idealization which is supported by Blatz[18] in describing the nature of biologic tissue.

One observes in Fig. 6 that the maximum stress occurs at x = 0.3. This means that as the membrane deformed, the maximum stress occurred at a point three-tenths from the center pole. This is the location where the fetal membranes tested most generally rupture (Fig. 7). For each of the fetal membrane samples used in the research, the stress distribution was determined for a deformation resulting from 10 mm Hg pressure application and subsequent increments.

With the use of the experimental data for the 66 membranes described earlier, the maximum longitudinal extension ratio (λ_1) and the maximum longitudinal stress (σ_1) for each membrane just prior to rupture was calculated. Also, the value of the extension ratio through the thickness of the membrane (λ_3) was calculated for each membrane specimen. The maximum calculated longitudinal stress is called stress tolerance of the membrane and is measured in kilograms per

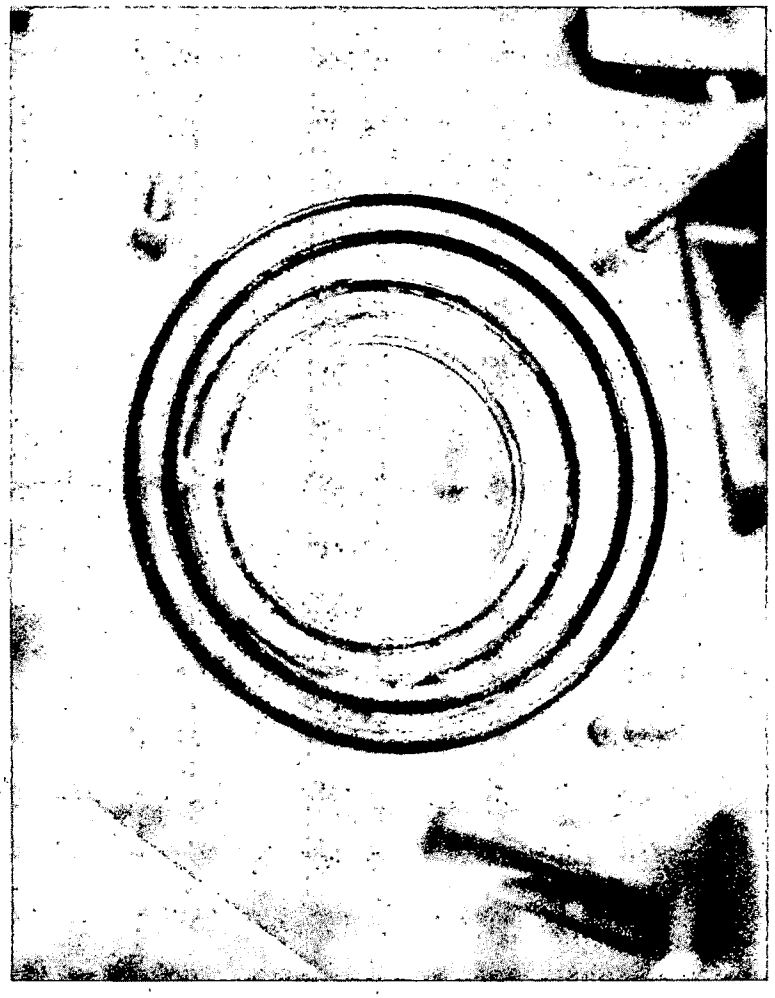


Fig. 7. Membrane after fracture with locus of rupture about 0.3 from center, the calculated point of maximum stress.

square centimeter. When the thickness of the membrane at the time of rupture is used to calculate the stress, stress tolerance is denoted by σ_{rr}.

The value of h_r (thickness at rupture) is calculated by considering the reduction in thickness resulting each time a pressure is applied to the membrane extending it elastically and causing it to creep. The creep extension is nonrecoverable. Hence, the reduction in thickness is regulated by the elastic extension ratio (λ_3) and the creep extension ratio (W_c/W_0). As one applies pressure from 0 to 10 mm Hg the nonrecoverable reduction in thickness is:

$$\Delta h = h_o \cdot (1 - \lambda_3) \cdot \frac{W_c}{W_o} \qquad (1)$$

and the resting thickness after the applied pressure on the membrane is reduced to zero becomes:

$$h_1 = h_o \cdot \left\{1 - (1 - \lambda_3) \cdot \frac{W_c}{W_o}\right\} \qquad (2)$$

That is, the initial thickness less the loss of thickness after the first cycle of pressure application. If one considers each 10 mm Hg increment of pressure application and reduction to be one cycle and the membrane ruptures in the nth cycle, the thickness of the membrane at the start of the nth cycle is:

$$h_r = h_o \cdot \left\{1 - (1 - \lambda_3) \cdot \frac{W_c}{W_o}\right\} n - 1. \qquad (3)$$

Also, in the nth cycle the thickness is further reduced by λ_3. Hence, the rupture thickness is:

$$h_r = \lambda_3 h_o \cdot \left\{1 - (1 - \lambda_3) \cdot \frac{W_c}{W_o}\right\} n - 1. \qquad (4)$$

When the maximum longitudinal stress (σ_1) is known for a pressure of 10 mm Hg the maximum stress at rupture can be calculated from the formula:

$$\sigma_{rr} = \frac{(\sigma_1)\,(n)\,(h_o)}{(h_r)} \qquad (5)$$

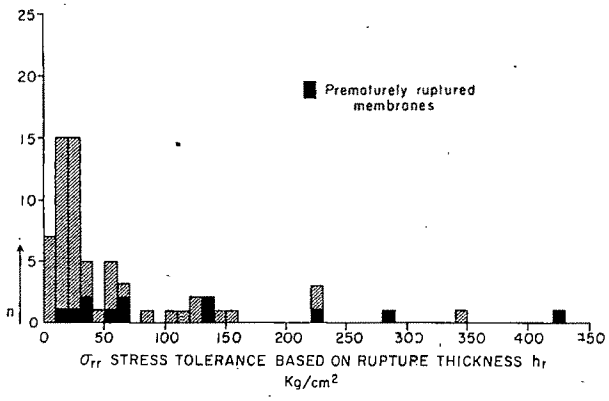


Fig. 8. Stress tolerance based on calculated thickness at time of rupture.

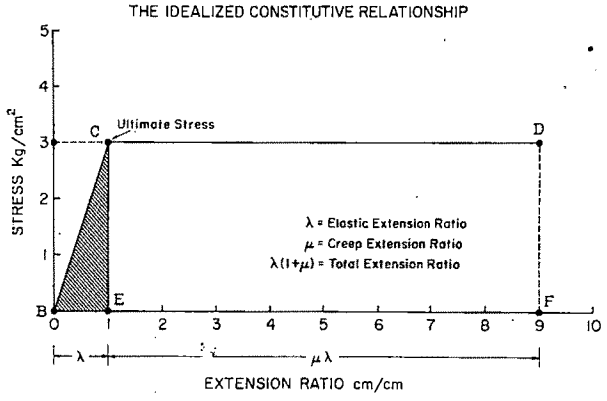


Fig. 9. Idealized relationship with the application of stress and response of creep and extension.

where n is the cycle during which rupture occurs. On the basis of Eq. (5) the stress tolerance based on the rupture thickness is calculated for the 66 membranes. The results are shown in Fig. 8. The solid parts express that number in the population which are preterm membranes.

Comment

The pressure at rupture data in our experiments agrees with the work done by Meudt and Meudt.[17] In their work, they found that the mean bursting pressure in their series of membranes studied was 399 mm Hg. The stress required to rupture the membrane increases not only with increasing pressure but also with the square of the diameter of the test sample. These authors[17] used diameters of 27 mm, whereas diameters of 76.2 mm were used in this research. The bursting pressure in our experiment should be approximately one-eighth of their values and this is indeed so.

Stress distribution and extension ratios are calculated quantities with the use of the experimental data. The method of calculation depends upon concepts and formulas which would be foreign to most obstetric readers. However, these concepts can be found in a recent publication.[16] The following discussion concerns an evaluation of stress and extension ratio distribution along deformed membrane surfaces.

When pressure is applied to the chorioamniotic membrane, the stretch which occurs develops internal stresses. These stresses resist the applied pressure and maintain the integrity of the membrane. Stress is an internal force divided by the cross-sectional area over which it acts and is expressed in kilograms per square centimeter. The total stretched extension of the membrane after pressure application is composed of two components, one of which is recoverable when the pressure is removed and the other of which is not recoverable. The recoverable component is called the elastic extension and the nonrecoverable component is called the creep extension. The percentage of deformation along any linear plan through the membrane relative to its original state is called the extension ratio. This extension ratio is measurable in three planes, namely, latitudinal, longitudinal, and transecting planes.

The elastic extension ratio is the elastic extension divided by the initial length. The ratio is expressed in centimeters per centimeter. The total extension ratio is defined as the total extension, i.e., the sum of the elastic extension and the creep extension divided by the initial length. The idealized relationship is demonstrated in Fig. 9. Here an application of pressure from point B toward point C will create the ultimate stress which a given tissue may be able to tolerate. This does not necessarily mean the point of fracture, for the material may continue to extend itself, i.e., from point B to points E and F, and maintain its integrity. It is only when point D is reached, that is, where the ultimate stress has been exerted and there is no more creep to be exhausted, that fracture occurs. Furthermore, in the range BE the extended material is totally recoverable. This is the nature of an elastic material. These two extension properties occur concomitantly in the experimental setting.

CD represents the creep extension of the material and the area enclosed in the rectangle CDFE represents the energy dissipated per unit volume during deformation. This energy is nonrecoverable and is lost with extension. The slope of the line BC represents the elastic modulus. This is the ultimate stress divided by the elastic extension ratio in the deformed material. This is the quality of the material to spring back to its original shape.

As the slope of the line BC increases, the elastic modulus will increase and the material will become

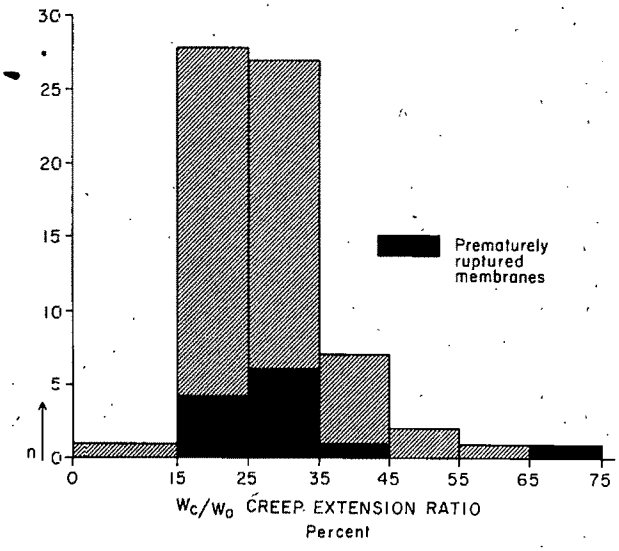


Fig. 10. Creep extension ratio represents the percentage of extension lost to nonrecoverable length (creep). Most membranes lose 15 to 45% of their elastic deformation.

stiffer. That is, there will be less recoverable extension for stress application. If equal forces are applied to two materials there is less extension in the material with a higher modulus. Also, as one stretches a material such as the chorioamniotic membrane, it will become thinner. If one removes the pressure prior to rupture, recovery will be determined by the size of the elastic extension ratio. The extension ratios demonstrated in the formula listed above are related to the thickness of the membrane at any given point. Thus, after any deformation of the membrane, it will become thinner than it was originally before the pressure application. That amount of nonrecoverable thickness is related to the nonrecoverable extension or creep.

If the membranes develop a high elastic modulus after several cycles of stretching and exhibit decreasing amounts of creep extension, it is possible that the stiffening phenomenon indicates that the material is being strain hardened. Following periods of strain hardening, the material ruptures quickly, losing its ability to creep.

The phenomena of extension, recovery, and creep (loss of recoverable material) are not sequential but concomitant. The above discussion represents an idealized picture of a dynamic biologic process. However, it does allow us a reasonable construct for the actual physical changes that occur.

Polishuk and associates[19] contended that membranes did not have a uniform tensile strength. This is consistent with biologic variability and is not an unexpected finding. Also, within any one sample of complex biologic material one should expect to find areas of local

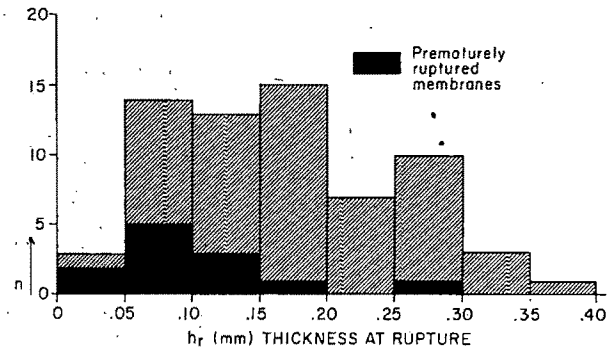


Fig. 11. Calculated thickness at rupture.

weakness which can decrease the tensile strength. Artal and associates,[4] employing an uniaxial extension apparatus, noted that there were no statistically significant differences in rupture tension between prematurely and spontaneously rupturing membranes. However, they did observe that prematurely rupturing membranes were thinner at the rupture site. These data were obtained by a microelectrode and are consistent with our calculated thickness.

The average values of W_c and W_0 are used to develop a W_c/W_0 ratio for each membrane. This value is the creep/extension ratio for the specimen. It represents the amount of nonrecoverable extension to recoverable extension. The bar graph in Fig. 10 shows the distribution of these ratios for the 66 membranes studied. The graph indicates that the majority of membranes have creep/extension ratios that fall between 15 and 35%. The grouping also shows that the percent of the nonrecoverable energy is not significantly influenced by gestational age. These data reflect the basic response of the membranes to stress applications and relaxation. They do not indicate how much stress was tolerated, however, by any particular membrane.

The data presented in Fig. 8 on stress tolerance are not in agreement with those of Polishuk. To the contrary, using our biaxial system, the preterm population was able to tolerate a greater stress application than the term membranes. Further data will be required to assess if this change is progressive throughout gestation. The difference in findings may be related to the calculation of stress tolerance based on the change in membrane thickness during stress application. Further, increasing gestational age may make membranes less tolerant of fracture, and preterm rupture could be primarily associated with local defects.

Such results lead us to believe that the membranes which clinically rupture prior to 37 weeks' gestational age are capable of sustaining higher stress application than those membranes which come to term. This was confirmed by analysis at the $p < 0.02$ level. However,

each of the preterm membranes used in the experiments did rupture prematurely between 28 and 36 weeks! Some flaw in those membranes at a local site or change in the character of a local area must account for the lowering of the stress tolerance at the time of rupture.

Stress tolerance involves many factors, significant of which is the reduction of thickness due to a sequence of pressure applications which takes place in the physiologic state of uterine contracture. With each pressure application, a deformation in the membrane results. Upon relaxation of the pressure only partial recovery is expected. Some permanent set remains in the membrane. Its dimensions may be larger in one plane but will thin out in others. The thinned section will now experience a greater stress when the pressure is reapplied. If the stress is too great, the membrane will rupture.

The preterm membranes thin out during the course of stress application to a greater degree than the term population. Their thickness was comparable prior to stress application with those membranes which spontaneously rupture at term.

This finding is not surprising when we recall that changing elastic moduli are related to membrane thickness. It could be postulated that during the course of pregnancy with recurrent stress applications (i.e., Braxton-Hicks contractions) and growth, a change occurs in the elastic moduli of the chorioamniotic membranes, making some of them "stiffer." When these term membranes are exposed to stress application, their tendency may be to fracture at a point of lesser thickness than the preterm membranes. Further work will be necessary to confirm this observation. However, to support this concept, there are two clinically observable processes which operate on "changing" the membrane thickness and enhancing the likelihood of rupture. These are commonly appreciated biologic stresses of pregnancy: (1) the inherent and chronic physiologic stress of growth and (2) the acute stress application of Braxton-Hicks contractions. Parry-Jones and Pyria[7] have described that after 28 weeks the intact fetal membranes are under tension. With the growth of the uterine cavity by term, this stretching extends the chorioamniotic sac to at least twice its resting size. Bourne[20] observed little mitotic activity after the first trimester in the membranes. On a molecular level accomodation to expanding growth requires adaptation to significant if gently applied growth stresses by cellular stretching rather than cell replication.

Alvarez and Caldeyro[21] have demonstrated that episodes of uterine contractions are physiologically present throughout pregnancy. Although these are often not of great intensity, we do find that membranes rupture after a series of recurrent low pressure applications. Toppozada and associates[22] studied patients in labor and observed that the contraction causing membrane rupture was not the strongest to which they were subject in 86% of cases. The results in Fig. 11 show that the preterm membranes have rupture thickness significantly ($p < 0.03$) less than term membranes. In our experiments and previous work[4, 6, 17] the rupture thickness of the amnion was the critical and final layer. This thinning to a greater degree suggests that in the preterm group there is greater ability to creep. There is less strain hardening than at term.

Fig. 11 demonstrates that the thickness at rupture of the membrane in preterm membranes is less than the thickness of term membranes. Hence, if local flaws in the chorion of these preterm membranes did exist, the stress placed on the amnion may have been far beyond the membranes' ability to tolerate the stress.

Separate functions are served by the chorion and the amnion. When they function in concert, the sac's integrity is maintained. Where there is dissonance in one member (presumably the chorion) the integrity is likely to fail. Early histologic investigation by Fetry[23] suggested weakness in the intermediate area of the membranes and that this shearing is the initiation of failure. Meudt and Meudt[17] took this up in their investigations. Neither chorion nor amnion alone could tolerate the mean bursting pressure which both together could tolerate. It would seem that different properties of the separate membranes serve distinct functions. Artal and associates[4] noted that there was reduced thickness near the site of prematurely rupturing membranes and Polishuk and associates[5] found weaker tensile strength at the rupture site. We contend that it is the change in thickness of the amnion when exposed to stress application, either chronic or acute, that predisposes to rupture. Further, once the point of ultimate stress is reached, recovery of elasticity is no longer available and fracture is imminent. Without support afforded by the chorion the amnion's stress tolerance is impaired by extension and will rupture.

The results of our research suggest the following model of the membrane rupture.

In certain cases, flaws develop in the chorion based on a phenomenon yet to be elucidated which prevent its appropriate elastic recovery. The physical properties demonstrated in this paper may well have biochemical correlates in tissue. The amnion is more resilient and returns to its original state more readily because of its biochemical and molecular constitution. As the chorion becomes progressively thinner, deforming by the physiologic stress of both growth and contractions, the

membrane ultimately exceeds its point of critical stress tolerance. The progressive thinning, with ultimate exposure of the amnion, leads to failure. This may occur at any time in gestation. The factors which account for this deficiency form the basis for further investigation.

Premature rupture of the membranes then may represent the concomitant effect of exagerated physiologic forces, i.e., increased contractions and growth and physical local defect which interfere with the naturally supporting roles of the chorion and the amnion.

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Management of prolonged pregnancy: Results of a prospective randomized trial

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Prolonged pregnancy was rigorously defined in 180 gravid women without other complications. Patients were randomly assigned to be serially followed, either by amniocenteses or by oxytocin challenge tests (OCT's). Induction of labor, based upon only (1) a finding of meconium in the amniocentesis group or (2) a positive test in the OCT group, was nearly three times more frequent in the amniocentesis group. The incidence of meconium, which overall was 22% initially and 44% at delivery, as well as the frequencies of obstetric and perinatal complications, were similar in both management groups. Although meconium was significantly associated with abnormal labor progression, intrapartum fetal distress, and low 1 and 5 minute Apgar scores, induction of labor after discovery of meconium, when compared to nonintervention, did not improve perinatal outcome. It is concluded that a search for meconium is of little value in the management of prolonged pregnancy. (AM. J. OBSTET. GYNECOL. 134:376, 1979.)

AN OTHERWISE uncomplicated pregnancy lasting 42 or more weeks is associated with a greater risk of perinatal death and morbidity than is a similar gestation completed at or near term.[1, 2] Recognition of this increased perinatal risk has led to a variety of schemes designed to improve fetal and neonatal outcome, but considerable disagreement regarding optimal management of prolonged pregnancy continues to exist for several reasons.[3] First, a prospective analysis of the precise causes of perinatal death and morbidity associated with this condition is not available. Also, the clinical definition of neonatal morbidity (i.e., "postmaturity syndrome") is subjective at best.[4, 5] In addition, proposed methods of antenatal fetal assessment and obstetric management have not been rigorously compared in published clinical trials. The obstetrician is therefore left in the unenviable position of trying to prevent possible perinatal death and disability with much advice—but little proved counsel—concerning problems that may or may not actually be encountered.

One characteristic feature of many prolonged pregnancies is meconium staining of the amniotic fluid which, when present, is said to be associated with even higher perinatal risk.[5–8] Because of the overall increased risk, and before biochemical or biophysical means were available to assess fetal well-being, antenatal discovery of meconium via amnioscopy or amniocentesis was interpreted as a sign of intrauterine compromise and therefore as an indication for delivery.[9–10]

Conceptual and practical problems exist if the management of prolonged pregnancy is based upon a search for meconium. Although meconium has been found to be associated with suboptimal perinatal outcome, its validity as an indicator of fetal distress is less well established. In the large series of patients reported by Saling,[11] 98.3% of the fetuses had normal scalp-

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blood pH values at the time meconium was detected during antenatal assessment. However, pH assessment was not done for those fetuses without meconium. More recently, Miller and associates[12] reported that intrapartum meconium in the absence of concurrent fetal heart rate (FHR) or acid-base abnormalities does not indicate fetal compromise. These results suggest that the suboptimal outcome associated with meconium may be unrelated to intrauterine distress, but instead to other events that may occur during labor and delivery (i.e., induction of labor with resultant hypoxia,[13] cesarean section,[14] or meconium aspiration[15]). Even if meconium were to be established as a valid and specific indicator of intrauterine compromise, its antenatal detection presents practical problems. Amniocentesis is an invasive procedure with a slight but finite fetal risk.[16, 17] In addition, both the normally decreasing volume of amniotic fluid after 36 gestational weeks and the oligohydramnios frequently encountered in prolonged pregnancy may make the detection of meconium technically difficult.

Taken together, these reasons suggest that an alternative approach to the management of prolonged pregnancy may be warranted. The oxytocin challenge test (OCT) has been suggested as a noninvasive means of assessing fetal well-being in a variety of high-risk obstetric conditions.[18] An uncontrolled clinical experience with 183 prolonged-pregnancy patients suggested that accurate fetal assessment was easily and safely accomplished with the OCT.[19] Moreover, the analysis of this experience revealed that the presence of antenatal meconium did not correlate with either a positive OCT or abnormal FHR patterns during labor. Therefore, for patients with prolonged pregnancy, a prospective and randomized clinical trial comparing the OCT and antenatal detection of meconium by amniocentesis was undertaken. This report summarizes the results of that trial.

Materials and methods

The trial was conducted between August 1, 1975, and July 31, 1976. At a suspected gestational age of 42 weeks, each patient was evaluated by one of the investigators; patients with other obstetric complications were excluded. A diagnosis of prolonged pregnancy was made if the menstrual history was reliable (i.e., the exact date of the last menstrual period was known, its duration and flow had been normal for that patient, and oral contraceptives had not been used within 3 months of that period), consistent with at least 42 gestational weeks, and confirmed by at least one of the following clinical assessments: (1) pelvic examination prior to 12 weeks; (2) ultrasonic cephalometry between 20 and 30 weeks; or (3) auscultation of unamplified fetal heart tones for at least 22 weeks. If the menstrual history was unreliable, a diagnosis of prolonged pregnancy was assigned if any two of these three clinical assessments were consistent with at least 42 gestational weeks.

The study protocol was explained and an informed consent was obtained. Based upon the last digit of the previously designated hospital number, women were then randomly assigned to be followed antenatally either by OCT's or by amniocenteses. These procedures were performed as previously described.[18, 20] Regardless of group assignment, each woman initially had an amniocentesis performed. Women followed by amniocenteses had the procedure repeated weekly unless meconium was discovered or no fluid could be obtained; in either case, they were admitted for induction of labor. Patients followed by OCT's had the procedure repeated weekly unless the test was positive, in which case they also were admitted for induction of labor. All inductions were conducted with intravenous oxytocin under surveillance of continuous, direct FHR and intrauterine pressure monitoring. Patients with clear fluid on amniocenteses or negative OCT's also had continuous, electronic monitoring whenever they presented with ruptured membranes or in active labor. Other management decisions during labor and delivery were made without consultation with or knowledge of the investigators conducting the antenatal assessments. Cesarean section was performed for the following indications: (1) inability to induce active-phase labor within 24 hours of beginning oxytocin, (2) arrest of cervical dilatation or arrest of descent in the presence of adequate uterine contractions,[21, 22] and (3) intrapartum fetal distress defined by recurrent late decelerations or severe variable decelerations[23] unresponsive to usual methods of intrauterine resuscitation.[24] Every meconium-stained baby was intubated and direct tracheal aspiration was performed.[15] Serum glucose was determined within 2 hours of birth and feeding was begun as soon after 2 hours as the condition of the infant permitted. Subsequent to admission into the clinical trial, seven patients (four in the amniocentesis group and three in the OCT group) either developed hypertension (3) or were found to have a breech presentation when admitted for labor (4). These late-developing problems were considered to possibly complicate data interpretation, and therefore these seven patients were not considered in the data analysis. Ninety patients thus remained in each group and the data from these were analyzed by chi-square test with Yates' correction; $P < 0.05$ was considered significant.

Table I. Comparison of obstetric and perinatal complications in patients with prolonged pregnancy managed by amniocentesis or OCT

Complication	Management group						
	Amniocentesis (N = 90)		P value	OCT (N = 90)		Total (N = 180)	
	No.	%		No.	%	No.	%
Induction of labor	29	32	<0.005	11	12	40	22
Abnormal labor*	13	14	NS	12	13	25	14
Fetal distress in labor†	11	12	NS	13	14	24	13
Cesarean section	11	12	NS	8	9	19	11
1 minute Apgar score <7	19	21	NS	12	13	31	17
5 minute Apgar score <7	6	7	NS	2	2	8	4
Fetal growth retardation‡	3	3	NS	4	4	7	4
Neonatal morbidity§	6	7	NS	7	8	13	7
Perinatal death	3	3	NS	1	1	4	2

*Defined by Friedman[21]: Prolonged latent phase, primary dysfunctional labor, secondary arrest of dilatation, or arrest of descent.
†Repetitive late or severe variable decelerations (see Methods).
‡Weight under tenth percentile for gestational age.[25]
§Hypoglycemia (serum glucose <30 mg/dl) occurred in 12 babies. One infant had Group B streptococcal sepsis.

Results

The group of women managed by weekly amniocenteses (N = 90) did not differ statistically from the group managed by weekly OCT's (N = 90) with regard to maternal age, parity, race, or neonatal sex ratio (data not shown). Likewise, the incidence of meconium at initial amniocentesis (22% overall) and at delivery (44% overall) was not statistically different, whether management was by amniocentesis (27% and 47% initially and at delivery, respectively) or by the OCT (18% and 41% initially and at delivery, respectively).

Obstetric and perinatal complications for the two management groups are compared in Table I. There were 2.6 times as many inductions of labor in the amniocentesis group (29/90 or 32% with meconium discovered antenatally) as in the OCT group (11/90 or 12% with an antenatal positive OCT, $P < 0.005$). By contrast, abnormal labor, fetal distress, cesarean section, low 1 and 5 minute Apgar scores, fetal growth retardation (below the tenth percentile for gestational age[25]), neonatal morbidity, and perinatal death occurred with similar frequencies in both management groups. Documented meconium pneumonitis did not occur in any infant. Neonatal hypoglycemia (serum glucose < 30 mg/dl) was significantly associated ($P < 0.05$) with fetal growth retardation and low 5 minute Apgar scores (data not shown). Three of the four perinatal deaths were due to lethal congenital anomalies; the fourth occurred in a meconium-stained, growth-retarded infant 2 hours following amniocentesis and while awaiting the availability of a fetal monitor so that induction of labor could begin. Postmortem examination failed to reveal a cause of death. Specifically, the amniotic fluid was not bloody, the cord-blood hematocrit was normal, and no hematoma of the cord or needle puncture of the baby could be identified. For the entire 180 pregnancies, combined perinatal death and serious morbidity (fetal growth retardation, low 5 minute Apgar scores, neonatal hypoglycemia, and sepsis) was 13% (24/180).

Compared to pregnancies where the amniotic fluid remained clear, those obstetric and perinatal complications occurring more frequently in the presence of meconium were (in order of increasing statistical significance): abnormal labor, intrapartum fetal distress, and low 5 and 1 minute Apgar scores ($P < 0.05$ to $P < 0.001$, Table II). The increased incidence of low 1 and 5 minute Apgar scores associated with meconium was not due to cesarean operations. Thus, compared to vaginal deliveries (with or without meconium) or to abdominal deliveries when the amniotic fluid was clear, cesarean sections performed in the presence of meconium were not associated with an increased incidence of low scores. For primigravid (but not parous) women with meconium, an increased incidence of low 1 minute Apgar scores was found if there was fetal distress in labor (7/11 or 64%) compared to those without distress (7/29 or 24%, $P < 0.05$). Although the occurrence of meconium did not significantly affect the overall cesarean section rate, primigravidas (10/40 or 25%) were more likely than parous women (1/39 or 3%) to be delivered abdominally if meconium was present ($P < 0.025$).

Table III demonstrates similar rates of obstetric and perinatal complications in patients with meconium, irrespective of antenatal management. Of the 42 amnio-

centesis-group patients ultimately proving to have meconium, labor was induced in 29 because meconium was detected by amniocentesis. Meconium developed in the 13 remaining pregnancies within the week following a clear amniocentesis, but before delivery occurred. Obstetric and perinatal complications were not statistically different in these two subgroups of patients with meconium who were followed by amniocenteses. Further consideration of the entire group followed by amniocenteses indicated nearly four times the rate of intrapartum fetal distress in women whose labor was induced because of meconium (7/29 or 24%) compared to women for whom labor was not induced (4/61 or 7%, $P < 0.05$).

Of the 24 OCT-group patients with meconium noted at initial amniocentesis, labor was induced only if and when the OCT became positive. As noted for the amniocentesis group, complication rates were not statistically different, irrespective of whether the meconium was first noted at initial amniocentesis or at delivery. A positive OCT was not associated with meconium, either at initial amniocentesis or at delivery (2/37 or 5% of patients ultimately proving to have meconium had positive OCT's and 9/53 or 17% of patients never having meconium had positive OCT's; $P > 0.2$).

Table IV shows the infrequent rates of obstetric and perinatal complications in the 44 OCT-group women who had clear amniotic fluid and negative OCT's throughout the study period.

Comment

The fetus participating in a prolonged pregnancy faces considerable risk as evidenced by the 13% incidence of perinatal death and serious morbidity demonstrated in this prospective study of carefully defined prolonged gestations. That this risk was not found to be even higher[5] may in part be attributable to continuous FHR monitoring of all patients during labor[26] and definitive management of airway meconium at the time of delivery.[15] Conversely, the lower perinatal risk suggested by other investigators[5] may have resulted from inclusion, among those studied, of pregnancies incorrectly identified as prolonged. A direct comparison of reported risk is difficult in the absence of uniform clinical criteria to define prolonged pregnancy.

The identification of meconium-stained amniotic fluid is somewhat more objective. Meconium was present in 22% of prolonged pregnancies at the time of initial entry into this study. The incidence of meconium increased to 44% by the time delivery occurred. Corroborating the increased perinatal risk previously reported,[1, 2, 5, 6] statistically significant increases in the

Table II. Relationship of amniotic fluid meconium to obstetric and perinatal complications in prolonged pregnancy

	Meconium present (N = 79)			*Meconium absent (N = 101)*	
*Complication**	*No.*	*%*	*P value*	*No.*	*%*
Abnormal labor	16	20	<0.05	9	9
Fetal distress in labor	17	22	<0.01	7	7
Cesarean section	11	14	NS	8	8
1 minute Apgar score <7	23	29	<0.001	8	8
5 minute Apgar score <7	8	10	<0.005	0	0
Fetal growth retardation	2	3	NS	5	5
Neonatal morbidity	6	8	NS	7	7
Perinatal death	4	5	NS	0	0

*Definitions of complications as in Table I.

Table III. Lack of impact of management method on obstetric and perinatal complications in prolonged pregnancies with meconium

	Management group				
	Amniocentesis (N = 42)			*OCT (N = 37)*	
*Complication**	*No.*	*%*	*P value*	*No.*	*%*
Abnormal labor	7	17	NS	9	24
Fetal distress in labor	9	21	NS	8	22
Cesarean section	6	14	NS	5	14
1 minute Apgar score <7	16	38	NS	7	19
5 minute Apgar score <7	6	14	NS	2	5
Fetal growth retardation	2	5	NS	0	0
Neonatal morbidity	4	10	NS	2	5
Perinatal death	3	7	NS	1	3

*Definitions of complications as in Table I.

Table IV. Obstetric and perinatal complications in 44 prolonged pregnancies with clear amniotic fluid and negative OCT's*

	No. and percentage of patients with complications	
Complications†	*No.*	*%*
Abnormal labor	3	7
Fetal distress in labor	1	2
Cesarean section	1	2
1 minute Apgar score <7	2	5
5 minute Apgar score <7	0	0
Fetal growth retardation	2	5
Neonatal morbidity	3	7
Perinatal death	0	0

*Pregnancies in the OCT management group which had negative OCT's and no meconium at any time during the study.

†Definitions of complications as in Table I.

frequencies of abnormal labor, fetal distress in labor, and low 1 and 5 minute Apgar scores were found when meconium was present. This study does not, however, answer the question of whether meconium directly causes or is simply associated with obstetric and perinatal complications. There is no doubt that neonatal death and morbidity can be directly caused by aspiration of meconium at the time of birth.[15] However, in this study the increased frequency of other obstetric and perinatal complications associated with meconium, despite the absence of a single instance of meconium pneumonitis, suggests that further study will be required to resolve this important question.

The demonstration of low oxygen saturations (15 to 25%) in umbilical vein blood following meconium passage[27] shows that meconium can be associated with intrauterine compromise. Observations such as these, together with the increased perinatal risk reported in the presence of meconium, undoubtedly led to the empirical practice of using meconium as an antenatal monitor of fetal well-being. In the absence of appropriate controls, the reports of favorable perinatal outcome when meconium was used as an indication for induction of labor[8-11, 27-30] are difficult to evaluate. In fact, the good results may have been due in part to the probability that the acid-base status was normal in nearly all of the fetuses at the time meconium was discovered.[11]

In the present study, the finding of meconium did not correlate with a positive OCT, and there was no increase in perinatal death and morbidity rates when induction of labor was avoided following antenatal detection of meconium. These results support and extend to the antenatal period the previous observations of Miller and associates[12] that in the absence of biochemical or biophysical evidence of hypoxia or asphyxia, meconium is of little consequence or significance to the fetus. Green and Paul[31] recently reported a large, retrospective experience with amniocentesis in prolonged pregnancy. They found no perinatal deaths associated with meconium, noted 10 perinatal deaths when there was no meconium at amniocentesis, and concluded that the test was of questionable value when used solely for the detection of meconium. Taken together, all of these findings suggest that meconium is not a sensitive or specific indicator of intrauterine compromise. In fact, it has been suggested that a fetus may pass meconium as a consequence of vagal stimulation or maturation of the gastrointestinal system and that this might account for the prevalence of this clinical sign in prolonged pregnancy.[12]

Amniocentesis or amnioscopy must be employed in order to establish a diagnosis of meconium during the antenatal period. The former procedure carries a small but finite fetal risk,[16, 17] whereas the latter is technically difficult and may cause rupture of fetal membranes.[9, 10, 32] The present study suggests that fetal well-being in prolonged pregnancies can be monitored effectively by a noninvasive and technically simple method—the OCT—without increasing obstetric and perinatal complications compared to monitoring by amniocentesis. Conversely, the results suggest that in order for amniocentesis to be as effective as the OCT, nearly three times as many inductions of labor—with an attendant increased rate of fetal distress—must be performed.

Two general considerations in the management of prolonged pregnancy emerge from this study. (1) Since improvement in perinatal outcome does not occur following induction of labor for meconium (compared to women with meconium followed by OCT's), the use of an invasive procedure for its detection (amniocentesis) is probably not warranted. The importance of avoiding the attendant risks of amniocentesis is further emphasized by the finding of a large subgroup of prolonged pregnancies (48% of those followed by OCT's, Table IV) which are essentially uncomplicated and at low risk. An important exception to this generalization may be the geographical necessity for delivery in an institution not equipped for continuous FHR monitoring or not having personnel available to insure adequate airway and subsequent neonatal management 24 hours a day. In this situation, discovery of meconium could facilitate maternal/fetal transfer to a better equipped and better staffed institution. (2) Although cervical status and the place of elective induction of labor was not directly addressed in this study, the data presented suggest management alternatives in this regard. Attempted induction with an unfavorable cervix may safely be avoided if fetal status can be monitored by the OCT. Furthermore, should uncertainty exist regarding length of gestation, awaiting the onset of spontaneous labor may prevent iatrogenic prematurity and its sequalae.[33] As noted previously, this recommendation remains unchanged regardless of the presence of meconium. However, the 22% of women who initially have clear fluid but then go on to develop meconium before delivery raises the question of whether elective induction of women without meconium could prevent the obstetric and perinatal complications associated with it. A randomized trial comparing induction of labor with expectant management under OCT control in women without meconium would be necessary to resolve this issue. However, since the presence of meconium and the status of the cervix need not be considered in prolonged pregnancies followed by

OCT's, maximal flexibility in planning patient management is assured.

Finally, since obstetric and perinatal complications do occur in prolonged pregnancy not accompanied by meconium or a positive OCT, continued research into alternative methods of fetal surveillance and obstetric management is necessary. The extremely low false-negative rate associated with the OCT[18] makes it an ideal research tool to be matched against other proposed methods of management in future controlled, clinical trials.

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Discussion

DR. ROBERT H. MESSER, Albuquerque, New Mexico. While it is generally recognized that the perinatal death rate is increased in prolonged pregnancy, there is not general agreement on the management of this obstetric complication. In fact, this controversy has been going on for many years. The rigorous definition of prolonged pregnancy employed by the authors lends credence to their conclusions. They have chosen a middle road between total noninterference and delivery by

one means or another of all prolonged pregnancies. This is a conservative course which recommends noninterference unless there is objective evidence of significant (perhaps life-threatening) distress, their evidence being the OCT. I agree with this approach.

Since the factors controlling the length of human gestation are still poorly understood, we have freedom to hypothesize. Let me propose an iconoclastic thought. Is it not possible that human pregnancy is sophisticated enough that the maternal-fetal unit adjusts to adversity, and that Mother Nature compensates by deviation from normal gestational length, and this actually serves to ameliorate outcome as long as survival occurs? Thus, in fact, might not some of the infants actually be better off left in the uterus? The natural tendency is to believe that because a pregnancy is beyond 42 weeks this state threatens the fetus and causes an increased perinatal death rate. Perhaps the shoe is on the other foot. Perhaps a threatened fetus prefers to stay in the uterus and the prolonged pregnancy is the result, not the cause, of an abnormal pregnancy. This would explain the higher incidence of anomalies as shown by Evans and also the increase in dysmature and undergrown infants shown by McClure Brown.

There are some examples which suggest that this may indeed be the case. It is estimated that late in pregnancy the fetal diet consists of the equivalent of 6 to 10 gm/kg/day of protein (amino acids, etc.) and is rich in 2- and 3-carbon sugars. Yet, my friends in neonatology tell me that they cannot exceed 3 to 4 gm/kg/day of protein, and 2- and 3-carbon sugars present high osmolality problems in neonatal nutrition. Even normal newborn infants *lose* weight in the first few days after birth, do they not? Why is it so hard to prove the logical-seeming idea that protein deprivation in economically depressed societies is the cause of high rates of premature birth, or the cause of mental retardation? As shown by Cheek and Hill, the primate has a remarkable capacity to protect fetal brain development from adverse effects of maternal protein deprivation as well as placental insufficiency induced by vascular occlusion. The children of the starved Dutch women of the Second World War are normal or superior intellectually.

In a fascinating and carefully controlled experiment, Riopelle and Hale[1] have recently shown that when primates are in an environment exposed partly to the elements, protein deprivation *prolongs* rather than shortens gestation. In fact, reduction of protein from 4 to 2 or 1 gm/kg/day lengthened gestation by 8.5 days, which is a 5% increase for the rhesus monkey. Perhaps even though things may not be going well, or perhaps because so, the primate fetus prefers to stay where he is.

As an incidental, I would like to ask the authors if they practice aspiration prior to delivery of the shoulders of meconium babies, since our experience has been similar to the Denver experience in dramatic reduction of meconium pneumonitis.

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DR. THOMAS H. KIRSCHBAUM, East Lansing, Michigan. Among gravidas with a pregnancy greater than 42 weeks in duration by presumably accurate history and physical examination, there is a small subset whose fetuses are destined to respond unfavorably to labor as manifest, retrospectively, by an increased incidence of fetal distress, of diminished Apgar score at birth, and of perinatal morbidity and death in comparison to pregnancies not so specified. The problem in management is to identify these postmature fetuses, minimizing false-positive errors which have the force of including normal infants simply the products of post-date pregnancies, and false-negative errors which enable postmature fetuses to fail to receive the special management they deserve. Further, the suspect pregnancies should be subjected to a course of management which will be effective in benefitting the postmature fetuses and not impairing the prospects for the post-date fetuses.

The authors, employing treatment protocols which employ the OCT and meconium staining on amniocentesis, have failed to define an effective treatment protocol. Their experience supports the contention of others that meconium staining of amniotic fluid is an insufficiently strong predictor of fetal distress in utero to be useful in this regard. Regrettably, their experience enables them justifiably to say little, if anything, about the usefulness of the OCT.

To be of clinical value, a test of antenatal well being must meet three requirements. (1) It must show a correlation with adverse perinatal outcome, a status which both meconium-stained amniotic fluid and a positive OCT enjoy. (2) The test must have a causal relationship strong enough to be a useful predictor of fetal distress in utero. That this is not the case for meconium-stained amniotic fluid has been known for several years.[1] The work reported here allows no comment in regard to the predictiveness of the positive OCT. (3) Therapeutic protocols must be shown to exist, employing the test, which suffice to lower perinatal morbidity and death rates.

In part, the negative result in this study is a function of experimental design. The authors have compared the use of the OCT as a predictor to meconium staining, not in comparison to simple expectant management. Therefore, only statements of relative, not absolute, value can be made about the OCT since management employing a useless indicator cannot be used as a standard against which to measure achievement. Experimental design is not structured to provide data which allow exploration of the validity of the OCT as a predictor of fetal distress in utero. Indeed, the author's contention that the OCT is an ideal research tool to be

used as a standard in evaluating new techniques for the diagnosis of fetal distress seems clearly incorrect. Though the incidence of false negative findings appears to be small, false positives have been reported in the range of 25% to 50% and speak against the usefulness of this determination except as a negative indicator. Since use of meconium staining as a predictor of fetal distress is known to be ineffective in reducing perinatal morbidity death rates, and results of the OCT do not differ significantly in this respect, all that can be said from the employment of the research protocol is that the OCT is equally useless. The choice of perinatal morbidity and death as an outcome measurement necessitates the employment of a complex function, not just of the utility of the OCT, but of the hazard of repeated amniocenteses, the induction of labor with various conditions of the cervix, and of the efficiency of intrapartum FHR monitoring.

In brief, the authors have failed to provide useful counsel based on rigorous data evaluation in a field marked, as they correctly point out, by too much unsubstantiated advice. Rather, they have added more advice of the same kind, and in so doing, they have joined several investigators who have contributed to an important problem in our discipline. Several techniques in fetal appraisal have been incorporated in clinical practice without rigorous objective proof of value as measured by their predictive strength and the prevention of perinatal morbidity and death. Some of these determinations have inappropriately in turn been used as standards by which to judge other newer techniques. Until such controlled objective appraisal of the value of the techniques for determining fetal distress in utero is made, advice based on opinion will continue to supplant counsel based on fact in the subspecialty of maternal and fetal medicine.

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DR. DAVID M. BARTON, Boise, Idaho. I would like to inquire about the comments concerning the value of estriol determinations following postmaturity or postdatism, and if some of the assumptions about well being, regardless of some of the parameters studied, would apply. I wonder about those cases of placental sulfatase deficiency and their increased incidence of postmaturity and how this might be correlated with the OCT.

DR. JOHN C. MORRISON, Memphis, Tennessee. While I concur with the comments of Dr. Kirschbaum as far as the analysis of data is concerned, I still think the literature would probably support the use of the OCT and perhaps the nonstress test in assessing gestations where meconium is present.

Also, I was impressed by the cases of the intrauterine growth retardation which Dr. Huddleston mentioned, and its relationship to possible fetal death. I would like to add a word of caution that in the pregnancy, postdates or otherwise, which may be complicated by intrauterine growth retardation, amniocentesis indeed may cause fetal distress by decreasing uterine blood flow. This situation may be similar to those at cesarean section where manipulation of the uterus appears to decrease placental blood flow through sympathetic stimulation. Perhaps fetal monitoring of patients after amniocentesis or other invasive techniques in the gestation complicated by suspected intrauterine growth retardation might be appropriate.

PROF. C. EUGENE MILLER, Louisville, Kentucky. From theoretical considerations we know that smooth muscle in the uterus produces a stress between 2.7 and 3.2 kg/cm.^{2} It appears that the magnitude of this stress is important in regard to the length of pregnancy.

I would like to know if in using the OCT challenge test the authors were concerned about such stresses and, if so, would they find acceptable the stress values quoted above?

DR. CHARLES A. WHITE, JR., Morgantown, West Virginia. I would like to ask about the group of patients that was followed by amniocentesis in which there was no evidence of meconium staining.

Am I correct in my assumption that this group did not exhibit any deaths during the next few days until the onset of labor? Was there any difference in the ability of that group of infants to tolerate labor as compared to those in which meconium staining was demonstrated?

DR. CROSBY J. EATON, Albuquerque, New Mexico. I wonder about the significance of the negative OCT test as much as I wonder about things like HPL and so on which I think have fallen by the way.

At our institution in Albuquerque, within a 3-week period, we had two patients in whom the fetuses died within 36 hours of a perfectly normal OCT because of prolonged pregnancy.

I do feel that this may be a useful tool, but I do not think that we can call it a totally reassuring thing to find a negative OCT test.

I would like to hear the comments of the essayists with respect to that.

DR. JAMES SEBASTIAN, Duluth, Minnesota. How long did you wait, 43 weeks, 44 weeks, 45 weeks? Could you comment on subgroups of inducible versus the unripe cervix in management? How long can we afford to wait if the patient is ready for delivery? What is the advantage of the place of delivery in more appropriate management of the fetus, including endotracheal aspiration of meconium for better fetal outcome?

DR. CHANG Y. LEE, Detroit, Michigan. During discussion, questions have been raised about false-positive and false-negative results of the contraction stress test (CST) or the OCT. If you review the OCT tracings, you may observe baseline FHR reactivity with accelerations with fetal movements in the "false-positive" OCT cases. In a few cases we have observed that the active fetus

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recorded late decelerations in response to occasional Braxton-Hicks contractions while also recording FHR accelerations with active movements during the performance of fetal activity *acceleration* determination (FAD) or nonstress test. In two cases, we performed a CST to observe the fetal response to uterine contractions during the CST and the results were positive. Since the baseline was reactive in these cases, we classified them as "reactive-positive" and considered them as false-positive tests. Both patients were delivered vaginally in good condition. Internal FHR monitoring had not recorded FHR signs of fetal distress in these cases.

A nonreactive negative test, a negative CST without baseline reactivity, did not give us a solid negativity. A case with a nonreactive negative CST had recorded persistant late decelerations with mild tachycardia during labor.

If we include the baseline reactivity in the interpretation of the CST, I think that we can eliminate most of the false-positive or false-negative readings.

DR. KNOX (Closing). I would like to say at the outset that I agree with Dr. Kirschbaum. I think that what we have presented is a statement of relative risk or relative benefit. Viewed from the point of relative benefit, I guess the ultimate question becomes whether the clinician chooses to use an invasive or a noninvasive tool to monitor prolonged pregnancies. The data presented clearly suggest the comparability, if not the superiority, of the noninvasive test.

I also concur with Dr. Kirschbaum that the OCT itself has never been validated in the way that he suggests appropriate (prospective, randomized trial with a nonintervention control group). Be this as it may, what has happened is that enthusiasm for this test (OCT) like many other previously touted forms of fetal assessment (HPL, estriols, etc.), becomes so widespread that, when investigators go to a Human Use Committee and ask if they may compare an OCT versus nonintervention or expectant management, they are told, "No; by denying the patient this test you would be performing an unethical study." I would suggest, and I assume Dr. Kirschbaum would agree, that through this type of reasoning we are perhaps doing the unethical thing by introducing therapies into our practice prior to having them well validated by appropriate, controlled studies. At any rate, admitting the fact that the OCT has not been given that kind of prospective validation, then the rationale for the use of the OCT in this type of study hinges on its very low false-negative rate (approximately 1/1,000 tests performed). Given the dilemma of a Human Use Committee that says nonintervention is not an acceptable alternative, we chose instead to use a diagnostic modality that at least has a very, very low false-negative rate.

I think that the current statement of relative risk being equal, and with amniocentesis being invasive and the OCT being noninvasive, the next step involves comparing the OCT to other proposed forms of management in prolonged pregnancy. I would reiterate that the noninvasiveness and low false-negative rate make the OCT a good choice to be matched with other therapies (e.g., induction of labor) in future studies of this clinical entity.

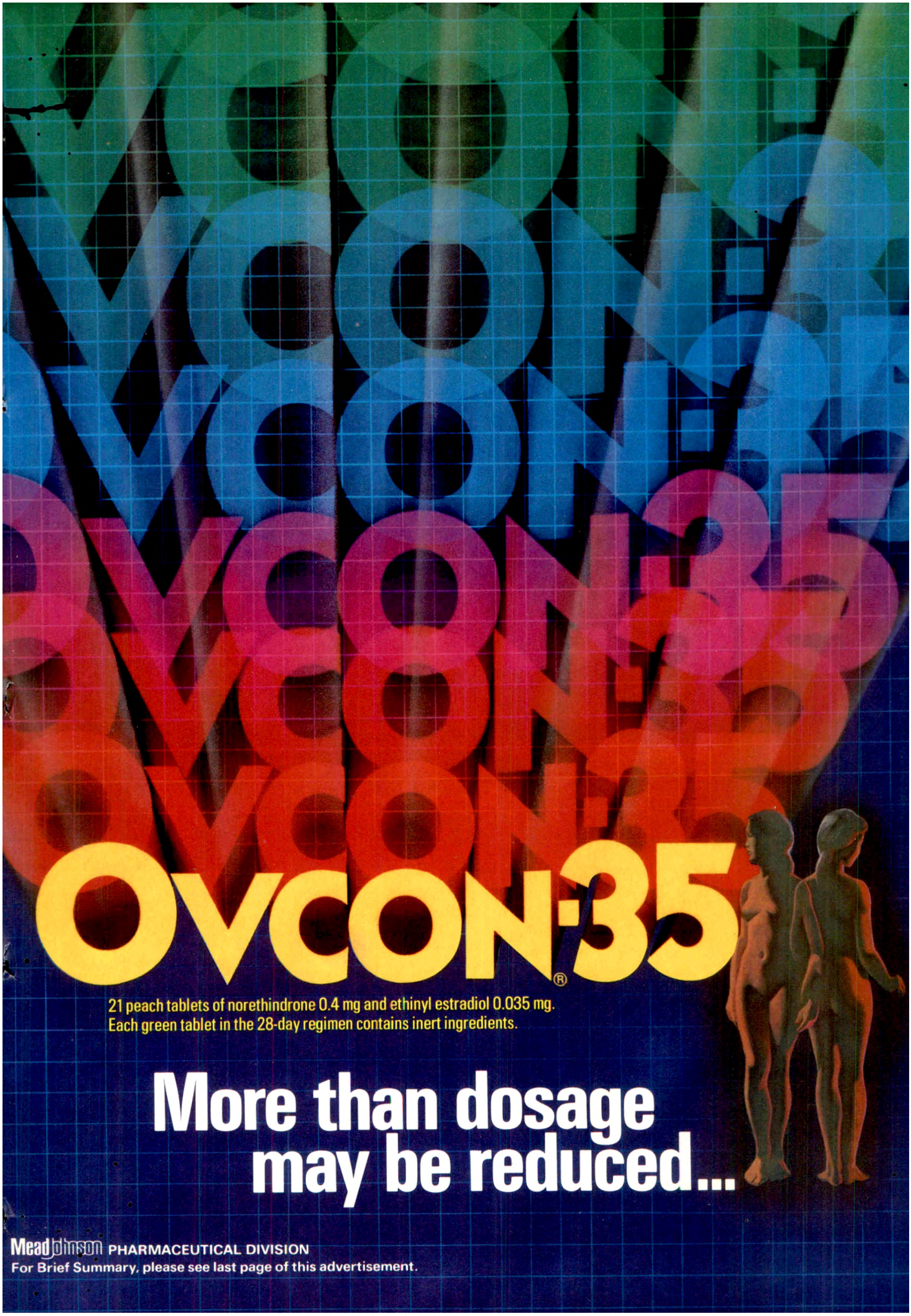
Dr. Sebastian questioned the place of elective induction in this study. This was not taken into account. No inductions were done except for the indications that were given. Clearly a question that now needs to be asked is: What happens if you follow patients expectantly with OCT's versus inducing labor at 42 weeks, perhaps using a good Bishop score as a starting point for entry into the study? That study is currently being completed, but in the current study this was not done.

Elective induction of labor likewise addresses another issue: When the incidence of meconium doubles between time of entry into the study (42 weeks) and its final termination (at delivery), can you prevent some of the complications associated with meconium by elective induction? I believe this needs to be answered in a well-controlled prospective study.

There was no difference in outcome whether the patient was delivered at 42, 43, and, in a couple of instances, 44 weeks, but the numbers are so small (at 44 weeks) that a final statement in this regard is not possible.

The comment about the reactivity of the fetus during an OCT as a possible means of eliminating false-positive tests remains, at this point, a hypothesis that needs to be further scrutinized. I was fascinated by Dr. Messer's hypothesis. It is always easier to comment about hypotheses and interesting speculation than to attempt to answer a good critique as put forth by Dr. Kirschbaum. Thank you, Dr. Messer, for taking us off the hook a little. The questions concerning fetal distress in the group that had no meconium and were followed by amniocentesis can be answered as follows: There were no specific problems in that group, but one could speculate that given the fact that there are some potentially positive OCT's in the group, and that if a positive OCT is viewed as a criterion of fetal distress, then if enough patients were studied, fetal distress would probably be eventually found. However, in the current study, no differences were found.

I would like to close by saying that in the group of patients with a negative OCT and no meconium (over 50% of all patients with prolonged pregnancy), the risk of complications to baby and to mother is extraordinarily low; as low as in a normal delivery population. Because of the extraordinarily low risk in this subgroup among all patients who have prolonged pregnancy, the goal ought to be to define fetal well-being in the least invasive and least therapeutically invasive method possible.



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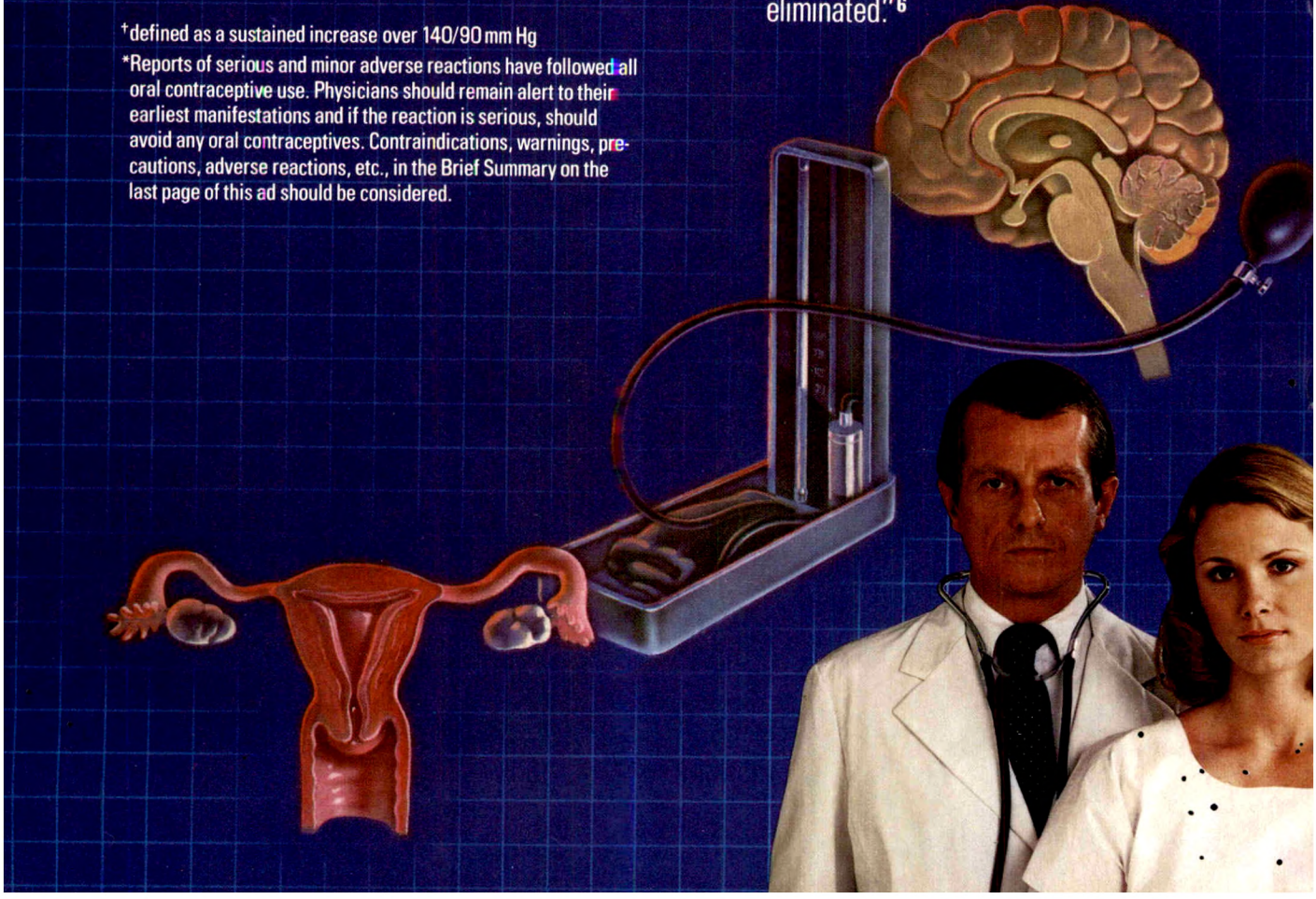
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Warnings:

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. Women who use oral contraceptives should be strongly advised not to smoke. Use of oral contraceptives is associated with increased risk of several serious conditions, including thromboembolism, stroke, myocardial infarction, hepatic adenoma, gallbladder disease, hypertension. Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks.

1) *Thromboembolic Disorders and Other Vascular Problems.* An increased risk of thromboembolic and thrombotic disease associated with use of oral contraceptives is well established. Three principal studies in Great Britain and three in the United States have demonstrated an increased risk of fatal and nonfatal venous thromboembolism and stroke, both hemorrhagic and thrombotic. These studies estimate that users of oral contraceptives are 4 to 11 times more likely than nonusers to develop these diseases without evident cause. In a study of cerebrovascular disorders in women with and without predisposing causes, it was estimated that the risk of hemorrhagic stroke was 2.0 times greater than nonusers and the risk of thrombotic stroke was 4 to 9.5 times greater. An increased risk of myocardial infarction associated with the use of oral contraceptives has been reported. Studies conducted in the United Kingdom found that the greater the number of underlying risk factors for coronary artery disease (cigarette smoking, hypertension, hypercholesterolemia, obesity, diabetes, history of preeclamptic toxemia) the higher the risk of developing myocardial infarction, regardless of whether the patient was an oral contraceptive user or not. Oral contraceptives, however, were found to be a clear additional risk factor. In terms of relative risk, it has been estimated that oral contraceptive users who do not smoke (smoking considered a major predisposing condition to myocardial infarction) are about twice as likely to have a fatal myocardial infarction compared to nonusers who do not smoke. Oral contraceptive users who smoke have about a 5-fold increased risk of fatal infarction compared to users who do not smoke but about a 10- to 12-fold increased risk compared to nonusers who do not smoke. The amount of smoking is a very important factor. British investigators concluded that the risk of thromboembolism including coronary thrombosis is directly related to the dose of estrogen used in oral contraceptives: preparations containing 100 mcg. or more of estrogen were associated with a higher risk of thromboembolism than those containing 50-80 mcg. of estrogen. The relative risk of thromboembolic disease associated with progestin-only oral contraceptives has not been determined. Cases of thromboembolic disease have been reported in women using progestin-only products, and they should not be presumed to be risk-free. The overall excess mortality rate annually from circulatory diseases for oral contraceptive users was estimated to be 20 per 100,000 (ages 15-35: 5/100,000; ages 35-44: 33/100,000; ages 45-49: 140/100,000), the risk being concentrated in older women, in those with a long duration of use, and in cigarette smokers. The highest risk was found in heavy cigarette smokers (15 or more cigarettes per day) who used oral contraceptives and were aged 40 or older. Women who smoke should be advised not to use oral contraceptives. The use of oral contraceptives in women over age 40 with other risk factors is not recommended. The mortality associated with all of the methods of birth control is low compared to the risk of childbirth, with the exception of oral contraceptive users who smoke and are over age 40. The lowest mortality is associated with the condom or diaphragm backed up by early abortion. The risk of thromboembolic and thrombotic disease associated with oral contraceptives increases with age after approximately age 30 and for myocardial infarction is further increased by hypertension, hypercholesterolemia, obesity, diabetes, or history of preeclamptic toxemia, and especially by cigarette smoking. The physician and the patient should be alert to the earliest manifestations of thromboembolic and thrombotic disorders (e.g., thrombophlebitis, pulmonary embolism, cerebrovascular insufficiency, coronary occlusion, retinal thrombosis and mesenteric thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately. If feasible, oral contraceptives should be discontinued at least 4 weeks before surgery of a type associated with an increased risk of thromboembolism or prolonged immobilization. 2) *Ocular Lesions.* There have been reports of neuro-ocular lesions such as optic neuritis or retinal thrombosis associated with the use of oral contraceptives. Discontinue the medication if there is unexplained sudden or gradual partial or complete loss of vision; sudden onset of proptosis or diplopia; papilledema; or retinal vascular lesions, and institute appropriate diagnostic and therapeutic measures. 3) *Carcinoma.* Long term administration of either natural or synthetic estrogen in certain animal species increases the frequency of carcinoma of the breast, cervix, vagina and liver. In humans, one study investigated the first 21 cases of endometrial adenocarcinoma in women on oral contraceptives reported to a registry. Of those women without predisposing risk factors for this disease, nearly all occurred in women who had used a sequential oral contraceptive. No evidence has been reported suggesting an increased risk of endometrial cancer in users of conventional combination or progestin-only oral contraceptives. No increase in breast cancer in women taking oral contraceptives has been reported although one study reported an increased risk of breast cancer in subgroups of women treated using oral contraceptives with documented benign breast disease. There is at present no confirmed evidence from human studies of an increased risk of cancer associated with oral contraceptives. Close clinical surveillance of all women taking oral contraceptives is essential. In all cases of undiagnosed persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be taken to rule out malignancy. Women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease or abnormal mammograms should be monitored with particular care if they elect to use oral contraceptives. 4) *Hepatic Adenoma.* Benign hepatic adenomas have been found to be associated with the use of oral contraceptives. One study reported a higher risk associated with oral contraceptive formulations with high hormonal potency. Although benign and rare, hepatic adenomas may rupture and may cause death through intra-abdominal hemorrhage. This has been reported in short term as well as long term users of oral contraceptives. Two studies relate the risk with duration of contraceptive use, the risk being much greater after 4 or more years of oral contraceptive use. While hepatic adenoma is a rare lesion, it should be considered in women presenting abdominal pain and tenderness, abdominal mass, or shock. A few cases of hepatocellular carcinoma have been reported in women taking oral contraceptives. The relationship of these drugs to this type of malignancy is not known at this time. 5) *Use in Pregnancy, Birth Defects in Offspring and Malignancy in Female Offspring.* Fetal abnormalities have been reported to occur in the offspring of women who have taken progestogens and/or estrogens during pregnancy. It has been shown that females exposed in utero to diethylstilbestrol, a nonsteroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare. A high percentage of such exposed women (30% to 90%) have been found to have epithelial changes of the vagina and cervix. Although these changes are histologically benign it is not known whether th condition is a precursor of vaginal malignancy. Male children so exposed may develop abnormalitie of the urogenital tract. Similar data are not available with the use of other estrogens but it cannot b presumed that they would not induce similar changes. The data suggest that the risk of limb reductio defects in exposed fetuses is somewhat less than 1 in 1000 live births. In the past, female se hormones have been used during pregnancy in an attempt to treat threatened or ha[illegible]abortio There is considerable evidence that estrogens are ineffective for these indications and there is n evidence from well-controlled studies that progestins are effective for these uses. Increases i chromosomal aberrations have been reported in women who become pregnant soon after ceasin oral contraceptive therapy. Embryos with these anomalies are virtually always spontaneous aborted. Whether there is an overall increase in spontaneous abortion of pregnancies conceived soo after stopping oral contraceptives is unknown. It is recommended that for any patient who ha missed two consecutive periods, pregnancy should be ruled out before continuing the contraceptiv regimen. If the patient has not adhered to the prescribed schedule, the possibility of pregnanc should be considered at the time of the first missed period and further use of oral contraceptive should be withheld until pregnancy has been ruled out. If pregnancy is confirmed the patient shoul be apprised of the potential risks to the fetus and the advisability of pregnancy continuation should b discussed in light of these risks. It is also recommended that women who discontinue or contraceptives with the intent of becoming pregnant use an alternate form of contraception for period of time before attempting to conceive. Many clinicians recommend three months Administration of progestin-only or progestin-estrogen combinations to induce withdrawal bleedin should not be used as a test for pregnancy. 6) *Gall Bladder Disease.* Studies have reported a increased risk of surgically confirmed gallbladder disease appearing after one year of ora contraceptive use and doubling of the risk after 4 or 5 years of use. 7) *Carbohydrate and Lipi Metabolic Effects.* A decrease in glucose tolerance has been observed in a significant percentage o patients on oral contraceptives. For this reason, prediabetic and diabetic patients should be carefull observed while receiving oral contraceptives. Increased serum levels of triglycerides and tota phospholipids have been observed in oral contraceptive users. The clinical significance of thi observation is unknown at this time. 8) *Elevated Blood Pressure.* An increase in blood pressure ha been reported in women receiving oral contraceptives. The prevalence of hypertension in ora contraceptive users may be no higher than nonusers in the first year of oral contraceptive use bu increases with longer exposure and in the fifth year of use is two and one-half to three times th reported prevalence in the first year. Women who previously had hypertension during pregnancy may be more likely to develop elevation of blood pressure when given oral contraceptives. 9) *Headaches.* The onset or exacerbation of migraine or development of headache of a new pattern which is re current, persistent or severe, requires discontinuation of oral contraceptives and investigation of th cause. 10) *Bleeding Irregularities.* Breakthrough bleeding, spotting and amenorrhea are frequen reasons for patients discontinuing oral contraceptives. In breakthrough bleeding, as in all cases o irregular bleeding from the vagina, nonfunctional causes should be borne in mind. In undiagnosed persistent or recurrent abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy. If pathology has been excluded, time or change to another formulation may solve the problem. Changing to an oral contraceptive with a higher estrogen content, while potentially useful in minimizing menstrual irregularity, should be done only i necessary since this may increase the risk of thromboembolic disease. Women with a past history o oligomenorrhea or secondary amenorrhea or young women without regular cycles may have a tendency to remain anovulatory or to become amenorrheic after discontinuation of oral contraceptives. Women with these preexisting problems should be advised of this possibility and encouraged to use other contraceptive methods. 11) *Ectopic Pregnancy.* Ectopic as well as intrauterine pregnancy may occur in contraceptive failures. However, in oral contraceptive failures, the ratio of ectopic to intrauterine pregnancies is higher than in women not using oral contraceptives since the drugs are more effective in preventing intrauterine rather than ectopic pregnancy. The higher ectopic-intrauterine ratio has been reported with both combination products and progestin-only oral contraceptives. 12) *Breast Feeding.* A small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs. The long-range effect to the nursing infant cannot be determined at this time.

Precautions: 1) A complete medical and family history should be taken prior to the initiation of ora contraceptives. Examination should include special reference to blood pressure, breasts, abdomen and pelvic organs, including Papanicolaou smear and relevant laboratory tests. As a general rule, ora contraceptives should not be prescribed for longer than 1 year without another physical examinatior being performed. 2) Under the influence of estrogen-progestogen preparations, preexisting uterine leiomyomata may increase in size. 3) Patients with a history of psychic depression should be carefully observed and the drug discontinued if depression recurs to a serious degree. 4) Because oral contraceptives may cause some degree of fluid retention, conditions which might be aggravated by fluid retention, such as convulsive disorders, migraine syndrome, cardiac or renal insufficiency or asthma require careful observation. 5) Patients with a past history of jaundice during pregnancy have an increased risk of recurrence of jaundice while receiving oral contraceptive therapy. If jaundice develops in any patient receiving such drugs, the medication should be discontinued. 6) Steroid hormones may be poorly metabolized in patients with impaired liver function and should be administered with caution in such patients. 7) Oral contraceptive users may have disturbances in normal tryptophan metabolism which may result in a relative pyridoxine deficiency. The clinical significance of this is yet to be determined. 8) Serum folate levels may be depressed by oral contraceptive therapy. This may complicate subsequent pregnancy with regard to folate deficiency. 9) The pathologist should be advised of oral contraceptive therapy when relevant specimens are submitted. 10) Certain endocrine and liver function tests and blood components may be affected by estrogen-containing oral contraceptives: a. Increased sulfobromophthalein retention. b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability. c. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T_4 by column, or T_4 by radioimmunoassay. Free T_3 resin uptake is decreased, reflecting the elevated TBG, free T_4 concentration is unaltered. d. Decreased pregnanediol excretion. e. Reduced response to metyrapone test.

Information for the Patient: Detailed Patient Labeling has been prepared for use by the patient and has been made available for distribution by the pharmacist.

Drug Interactions: Reduced efficacy and increased incidence of breakthrough bleeding have been associated with concomitant use of rifampin. A similar association has been suggested with barbiturates, phenylbutazone, phenytoin sodium and ampicillin.

Adverse Reactions: An increased risk of the following serious adverse reactions has been associated with the use of oral contraceptives (see **Warnings**): Thrombophlebitis, pulmonary embolism, coronary thrombosis, cerebral thrombosis, cerebral hemorrhage, hypertension, gall bladder disease, congenital anomalies. There is evidence of an association between the following conditions and the use of oral contraceptives, although additional confirmatory studies are needed: Mesenteric thrombosis; benign hepatomas; neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis. The following adverse reactions have been reported in patients receiving oral contraceptives and are believed to be drug related: Nausea and/or vomiting, usually the most common adverse reactions, occur in approximately 10% or less of patients during the first cycle (Other reactions, as a general rule, are seen much less frequently or only occasionally.); gastrointestinal symptoms (such as abdominal cramps and bloating); breakthrough bleeding; spotting; change in menstrual flow; dysmenorrhea; amenorrhea during and after treatment; temporary infertility after discontinuance of treatment; edema; chloasma or melasma which may persist; breast changes (tenderness, enlargement, and secretion); change in weight (increase or decrease); change in cervical erosion and cervical secretion; possible diminution in lactation when given immediately postpartum; cholestatic jaundice; migraine; increase in size of uterine leiomyomata; rash (allergic); mental depression; reduced tolerance to carbohydrates; vaginal candidiasis. The following adverse reactions have been reported in users of oral contraceptives, and the association has been neither confirmed nor refuted: Premenstrual-like syndrome, intolerance to contact lenses, change in corneal curvature (steepening), cataracts, changes in libido, chorea, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption, vaginitis, porphyria, impaired renal function.

Acute Overdosage: Serious ill effects have not been reported following acute ingestion of large doses of oral contraceptives by young children. Overdosage may cause nausea, and withdrawal bleeding may occur in females.

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Female sex hormone receptors and their importance in clinical practice

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We now know a great deal about the early steps in the induction of a steroid hormone response at the cellular level. This helps to explain some of the observed clinical responses and also the development of some congenital anomalies. The importance of progesterone as a balance to the proliferative effects of estrogen both in hormone replacement therapy and in the hormone-sensitive tumors is clear. It is hoped that further studies will guide us to ways in which we might enhance these benefits. (AM. J. OBSTET. GYNECOL. 134:385, 1979.)

THERE ARE TWO broad categories of action of the steroid hormones. There is first a series of not very well defined nor easily measurable general effects upon the whole animal, often mediated by other hormones or enzyme systems. Such effects are seen in patients suffering from premenstrual depression[1] and it is through such general mechanisms that the beneficial effects of estradiol on the reticuloendothelial system are produced.[2, 3] Many of the problems attributed to the withdrawal of estrogen in the postmenopausal woman are attributed to loss of support for such general mechanisms.[4]

The second category is concerned with the highly specific and more easily measurable effect upon what are commonly called "target tissues." In the past a "target tissue" was defined as one that showed a clear, predictable, and often dramatic response to stimulation with the appropriate hormone. Today we can redefine this term because the presence of adequate amounts of highly specific receptor protein is in most cases mandatory if a cell is to be responsive to a steroid hormone.[5, 6] These data are so convincing that we can say with certain qualifications that if a particular steroid receptor is present in abundant amounts then that cell will respond to that steroid.

The qualifications relate to certain situations in which cells do contain soluble receptor but have defects in the machinery through which the receptor-steroid complex usually operates.

Blood plasma does contain specific, high-affinity, steroid-binding proteins which are of considerable importance in that they do bind appreciable amounts of steroid and make them physiologically inactive. However, these proteins have properties and functions which are noticeably different from the intracellular binding proteins with which we are at present concerned.

As gynecologists we are most concerned with the female sex steroids and, in fact, for practical reasons, most of the work on receptors has been done in relation to estrogen and progesterone. However, many of the general conclusions relate to the androgens, the glucocorticoids, and the mineralocorticoids as well.

Estrogen receptors

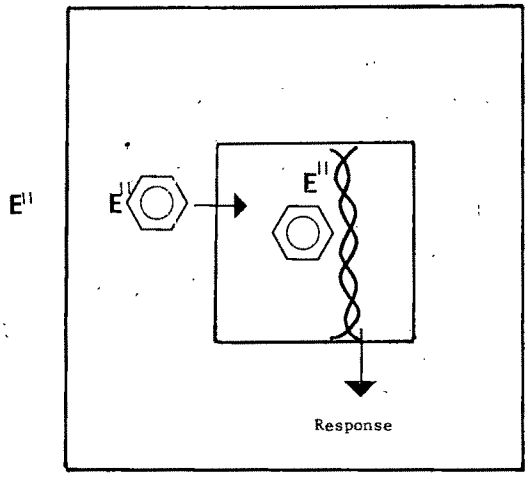
The concept of drug-receptor reaction was formulated at the turn of the century by Paul Ehrlich and it has since been modified to explain many of the actions of drugs and hormones.

Early attempts to test the validity of these ideas in relation to steroid hormones were unrewarding because pharmacologic doses of the hormone had to be administered to detect it at the cellular level by the methods then employed. The advent of tritium-labeled steroids enabled researchers to administer physiologic amounts of steroid, observe the way it behaved in body fluids, follow it into tissues, and detect its presence within various components of cells. This revolutionized experiments and led to the production by Jensen and Jacobsen[7] of a general model explaining the intracellular movement of estrogen within a responsive cell (Fig. 1).

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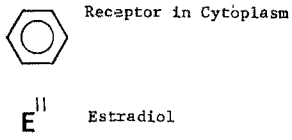


Fig. 1. Hypothetical model for estrogen interaction within the endometrial cell.

The steroid enters the cell and combines noncovalently with a limited number of specific receptor molecules of high affinity. This complex then enters the nucleus and elicits a response.[5] The response is determined by the nature of the reacting cell, not by the estrogen. Thus, whereas cells of the human endometrium respond to estrogen by proliferating, secretory cells of the endosalpinx respond by producing a characteristic fluid. We thus have the idea of an estrogen-receptor complex as a switch or amplifier.[8]

Every steroid receptor so far discovered is an oligomeric protein, the composition of which is dependent upon ionic strength. Changing salt concentration from 10 mM to 400 mM KCC changes the molecular weight of the receptor from about 2×10^5 (7 to 8 S) to 70,000 (4S). There is evidence that this change in size of the molecule also occurs when the receptor-steroid complex moves into the cell nucleus.[8] This led Jungblutt[9] to propose a refinement of Jensen and Jacobsen's model. He suggested that the primary receptor in the cytoplasm had two components (Fig. 2). One of these components (4S) with the steroid moved into the cell nucleus to constitute the nuclear receptor.

The number of cytoplasmic receptor molecules has been calculated to range from 1,000 to 9,000 per cell in the human endometrium and endosalpinx.[8] The number increases in response to estrogen stimulus.[10] The

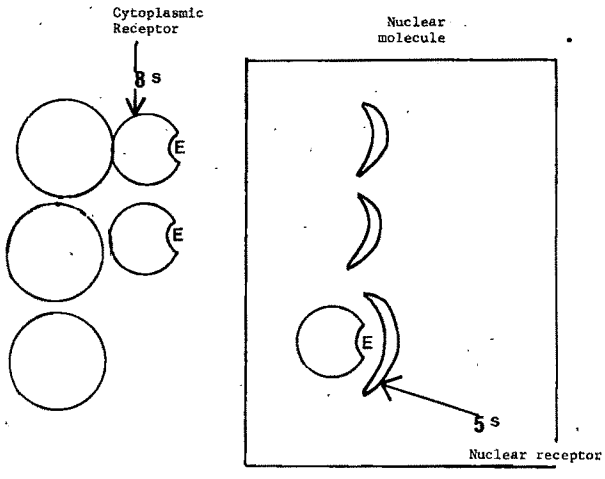


Fig. 2. Hypothetical model for estrogen transport into the nuclei of target cells. (Modeled after Jungblutt.[9]).

calculated binding constant (mean 3×10^{-13}) in both endometrium and endosalpinx indicates that the receptor molecules have a very high affinity for their respective steroids.[8] Comparatively minor changes in the steroid molecule decrease the binding affinity of the receptor. A change from estradiol-17β to estrone, for example, lowers the affinity by about 90%.[5]

The movement of the steroid-receptor complex to the nucleus results eventually in its attachment to chromatin. This over-all process is temperature dependent.[5] It is accepted that the steroid-receptor complex must be activated before becoming attached to chromatin but the nature of this process and the site at which it occurs are uncertain. Further, the identity of the nuclear acceptor for the steroid receptor remains a matter of dispute. It does appear that DNA-receptor interactions are physiologically important[11] but it is unlikely that such an interaction could explain all of the nuclear events. There is evidence that a specific nonhistone protein(s) is important in determining the number and tissue specificity of acceptor sites.[12, 13]

The picture is further confused by the possibility that the DNA sites so far measured represent comparatively low affinity binding and that there are a smaller number of very high affinity sites yet to be discovered. The exact location of the nuclear acceptor site is of more than academic interest because it may be expected to throw light on the issue of whether estrogen is a switch or an amplifier. If it acts as a switch the acceptor sites could be located in regions of inactive chromatin, but as amplifiers the acceptors might be found in more active regions of the chromatin. This is of some importance in clinical consideration of hormone-sensitive tumors. Both "switch" and "amplifier" processes may occur depending upon the tissue being considered.

Progesterone receptors

Cytoplasmic receptors specific for progesterone have been investigated by means of the same techniques as are employed in estrogen receptor studies. Much that has been said of estrogen receptors can be said for progesterone receptors also. Of greatest interest to the clinician is the interaction of the two steroids and their receptor complexes at the cellular level. While the number of estrogen receptors is autoregulated,[14] the number of progesterone receptors in many (though not all) progesterone-sensitive cells is determined by estrogen.[15] This serves to explain the synergistic effect of the two hormones. Equally relevant to the clinician is the observation that progesterone and certain progestational agents appear to affect the way in which the estrogen-receptor complex is translated to the nucleus of the target cell. It has been shown that while 80 to 90% of tritium-labeled estradiol-17β which enters the cell during the follicular phase of the menstrual cycle or in endometrium subject only to estrogen stimulation becomes associated with cell nucleus, only 20 to 30% becomes similarly associated during the luteal phase of the cycle or when the endometrium is subject also to progesterone or progestational agents.[8, 15] The mechanism by which this shift in the intracellular distribution of administered estradiol is brought about is not known, but progesterone has been shown to bring about changes in the lipid layers which surround the nucleus. These may be important in determining the ease with which the estrogen-receptor complex reaches the nucleus.[16]

Androgen receptors

Again, much that has previously been said can be applied to androgen receptors. They too are autoregulated,[17] which perhaps explains the sensitivity to low blood levels of androgen seen in patients treated and "cured" in the polycystic ovary syndrome. Apart from the uncommon virilizing syndromes, the chief interest of the gynecologist in androgens and their receptors is in the field of normal sexual development. In utero, the fetus with an XY chromosome pattern shows regression of the müllerian duct and the development of the wolffian duct into vas deferens, epididymis, and seminal vesicle. The external genital anlage develops into the prostate gland and the external genitalia. Virilization of the wolffian duct is achieved by testosterone in the absence of dihydrotestosterone (DHT) but normal development of the external genitalia requires the presence of DHT, not testosterone. These processes require the presence of androgen receptors.[18] In the autosomal recessive mutation in which 5α-reductase activity is low in the precursors of the external genitalia, external masculinization does not occur because no DHT is formed. As normal amounts of testosterone circulate, structures derived from the wolffian duct are formed normally. Other mutations are known in which the absence of androgen receptors results in failure of both müllerian and wolffian structures despite an XY genotype and normal levels of blood testosterone. Female external genitalia develop and give rise to the condition we call testicular feminization.[18]

What significance does this steroid-receptor knowledge have for the clinician?

1. Understanding of the initial steps in the mechanism of hormone action has helped us to understand the way in which certain maldevelopments of the secondary sex organs is brought about, without enabling us to do anything to prevent abnormality at present. We need to look further to find the cause of the enzyme defects which are responsible for such failure of normal hormone conversion as we see in testicular feminization.

2. The fact that we visualize estrogen as operating a "switch" or "amplifier" mechanism means, I think, that we should not regard estrogen as a substance causing malignant mutations but as one promoting growth in tumors which remain hormone sensitive. Not all receptor-positive tumor cells are hormone responsive,[11, 20] but the presence of receptors remains a very strong indication of responsiveness. The presence of receptors always indicates that the cells concerned are derived from responsive antecedents. This can be useful in determining the origin of tumors when the histologic examination is unhelpful (e.g., ovary vs. endometrium).

3. The distinction between a carcinogen and a tumor-promoting substance may at present be academic. Estrogen therapy after the menopause can be expected to give rise to an increased incidence of clinical malignancy in the endometrium in either case. In practice, the observations of the effect of progesterone on estrogen-sensitized cells (as well as the histologic evidence) should suggest that progesterone can protect against clinical malignancy when estrogen is given in the treatment of postmenopausal women. Clearly the hormones should be given cyclically to imitate the normal pattern of ovarian steroid production, since progesterone receptors appear in significant amounts only when the responsive cell is prestimulated by estrogen.

4. The fact that estrogen functions by forming a local complex in "target" cells should indicate that local application of the steroid would produce its effects. This is true, for local applications of estrogen-cream

bring about maturation of vaginal epithelium atrophied after the menopause. There is evidence (Taylor and Brush: Unpublished) that local application of estrogen—approximately 1/100 part of the normally recommended dose—can produce local maturation of vaginal epithelium without spilling over into the general circulation to cause unwanted effects such as cystic glandular hyperplasia.

5. Although the presence of minute amounts of receptor in target cells is genetically determined, the amount increases only slowly to the high levels seen in the reproductive years. Once present, it never completely disappears, although it diminishes as hormone stimulation ceases. This explains the relatively slow development of the secondary sex organs at puberty and the potential for hormone response that remains after the menopause. Radiation does not interfere with the presence of cytoplasmic receptors[8] and there is therefore the prospect that both radiation and hormone therapy can be applied with benefit in the treatment of hormone-dependent malignancy.

6. I was particularly asked not to dwell upon the use of hormone receptor studies in relation to cancer, but no review of their value to the clinician would be complete without mention of this. In the uterus and fallopian tube, where receptor protein abounds, malignancy is virtually always hormone sensitive. In the ovarian adenocarcinoma, where it is absent, no benefit is obtained from hormone treatment of any sort. Endometrial carcinoma always responds to estrogen deprivation which follows oophorectomy by showing a slower rate of growth and often, too, the shrinkage of secondary deposits. More important practically is the positive response seen in such tumors and secondaries following administration of progestational agents.[20, 21] The tumor cells pass from a proliferative to a secretory phase histologically and the proportion of administered estradiol reaching the cell nucleus falls from 80% to 30%. These responses are best seen in premenopausal women with normal levels of circulating estrogen, as one would expect from knowledge of the behavior of progesterone receptor. This has led some units, such as my own, to try to induce a similarly enhanced response in postmenopausal women, whose progesterone receptors are comparatively inactive, by administration of estrogen before the progestational agent. Insufficient data are at present available to encourage this form of approach but it is clear that progestational agents are an adjunct to surgery and radiotherapy and in my view should be given from the time the diagnosis is made until at least 3 months after it is thought that treatment is complete.

In breast cancer the results of receptor studies have not been as clearcut as in endometrial cancer. In view of the pleomorphic nature of the breast tumors this is not surprising. However, the premise that receptor assays would predict the response of the tumor to endocrine therapy has partially stood the test of time. Tumors having low or undetectable levels of receptor have less than a 10% chance of responding to endocrine treatment. However, only 50 to 60% of tumors with good amounts of receptor respond well to endocrine treatment, perhaps because there are abnormalities in the response machinery beyond the receptor stage. It is clear that patients with receptor-negative primary breast tumors develop recurrent disease at about twice the rate of their receptor-positive counterparts. This may simply reflect the greater maturity of the latter cells, but studies of the possibility of inducing receptor in receptor-negative tumors would seem to be appropriate.

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Autonomic hyperreflexia in pregnancy and labor: A case report

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The course of pregnancy and labor in a 36-year-old quadriplegic primipara is described. The associated problem of autonomic hyperreflexia and its management is discussed.
(AM. J. OBSTET. GYNECOL. 134:390, 1979.)

AS THE NUMBERS of automobile accidents and other diverse injuries from trauma increase there is now a rising incidence of severe spinal cord damage. The improved acute and long-term care of these individuals has led to greater longevity and transformation in their outlook from an inevitable hopelessness to that of an expectation of a near-normal and productive life. There is no longer any reason to discourage young spinal-injured women from either marriage or motherhood. Experience has shown that they are able successfully to continue pregnancy to term.[7, 11, 15] Obstetricians, therefore, should be aware of the peculiar problems and definite hazards to the mother and to the fetus.[4, 6] Guttmann, Frankel, and Paeslack[7] have called attention to the danger of pressure sores, anemia, and urinary tract infections during pregnancy, but special attention is directed to the problem of autonomic hyperreflexia, which may be more serious and can be life threatening, particularly during the third trimester and delivery, unless recognized promptly and managed correctly.

The syndrome of autonomic hyperreflexia, dysreflexia, or spinal poikilopoiesis[12] was first recognized by Head and Riddoch[10] in 1916 as a serious problem in the management of patients with spinal cord injuries. The potential for vital danger to the injured patient has been stressed by various authors.[1, 2, 8] Severity ranges from symptomatic annoyance to hypertensive encephalopathy,[18] cerebrovascular accidents, and death. Primarily affected are patients with a cord injury at the level of the sixth thoracic vertebra and above, that is, above the level of the splanchnic outflow, who lose hypothalamic control over their sympathetic spinal reflexes. It occurs only in patients with viable distal cord segments below the level of the disruption and may also be observed with incomplete lesion.[2] Generally, starting within a few months after the spinal shock recedes, the storm is produced in susceptible patients by any of several noxious stimuli below the level of the lesion. Afferent stimuli arising in the bladder, bowel, and genital areas ascend in the spinothalamic tracts and posterior columns. Reflex motor outflow through neurons originating in the lateral horns causes vasoconstriction and consequent hypertension. The patient experiences severe pounding headaches, has blood pressure elevations ranging as high as 250 mm Hg systolic and 150 mm Hg diastolic, bradycardia, flushing, sweating, tingling, and nasal stuffiness. The characteristically intense pounding headaches come from the stretch of the intracranial pial arteries because of the increased blood pressure at a time when supraspinal regulation to reduce blood pressure is impossible since the efferent pathways are interrupted.[17] Flushing (above the level of the lesion), sweating, bradycardia, and nasal stuffiness have been interpreted as adaptive mechanisms.[8] Bors and Comarr[2] have observed that these manifestations are more sustained and prolonged following bladder stimulation than with rectal stimulation. They tend to diminish as the stimulus is withdrawn. The following case is reported to illustrate hyperreflexia in a tetraplegic pregnant woman.

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Case presentation

A Navajo Indian woman had become tetraplegic (complete loss below the level of the sixth cervical vertebra) following an automobile accident at 16 years of age. She was successfully rehabilitated and gainfully employed as a switchboard operator. At 35 years of age she married, then soon conceived after she and her husband obtained detailed advice from her physicians of the physical and sexual aspects of the marriage, and encouragement and support in the advisability of having a child. The prenatal course was normal until the thirtieth week. The hemograms remained stable and pulmonary function studies were normal within predictable tetraplegic parameters. Bladder management was meticulous. An indwelling urethral catheter was changed weekly; methenamine mandelate (Mandelamine) 1 gm q.i.d. and ascorbic acid 1 gm q.i.d. were given for urinary antisepsis. There were no episodes of clinical urinary tract infection. Normal bowel function was managed by anal sphincter dilatation and suppositories.

At 30 weeks' gestation the patient complained of mild headaches which were relieved by changing the plugged catheter. Because of increased frequency of micturition and a rise in blood pressure to 180/100 mm Hg, the patient was treated with oxybutinin chloride (Ditropan) 5 mg t.i.d., and triple anesthesia (topical anesthesia of the urethral, rectal, and vesical mucosa) during anal dilatation and catheter changes. This suppressed the headaches and the blood pressure stabilized at around 100/70 mm Hg.

At 36 weeks the frequency of headaches increased and the blood pressure rose again. She was hospitalized for observation and stabilization until delivery. An episode of urinary tract infection was successfully treated with intravenous carbenicillin. At this time the slightest manipulation of the catheter or a routine pelvic examination led to pounding headaches, sweating, flushing, and a sudden rise in blood pressure. The oxybutinin chloride and triple anesthesia were continued and guanethidine 25 mg daily was instituted. For the next 10 days the cervix had effaced somewhat, but the blood pressure remained labile, and the episodes of headache, though controlled in severity, kept increasing in frequency. Consequently, in week 38 of gestation it was decided to evacuate the uterus. Continuous epidural anesthesia was instituted; amniotomy was performed and intravenous infusion of Pitocin was begun. Though good uterine contractions developed, the autonomic hyperreflexia became quite intense; the diastolic blood pressure regularly reached 120 mm Hg. The hyperreflexia remained nonresponsive despite repeated injections for the epidural anesthesia. In the time intervals between contractions the blood pressure returned to normal. After 8 hours and only minimal progress the infant was delivered by primary cesarean section. Spinal anesthesia produced an immediate reduction in blood pressure to normal and complete remission of the physiologic turbulence. A living female infant, weight 3,352 grams, with Apgar score 9, was born. The puerperium was uneventful and the patient was discharged to her home after a week.

Comment

The relationship between autonomic hyperreflexia and uterine contraction was postulated by Guttmann and has been reported by several authors.[7, 15, 16] Comarr[4] suggested that the hypertension assoicated with this syndrome differed in etiology from that of preeclampsia, and should be managed differently. It has been observed that the symptoms of autonomic hyperreflexia are clearly related to the uterine contractions and decrease or even disappear during uterine diastole, the resting period between contractions.[15] They disappear completely at the end of the third stage of labor, as illustrated above. Signs of autonomic hyperreflexia during bladder and bowel contractions in pregnancy should be expected to become exacerbated in the course of labor and delivery. The physician should be alert to recognize this and provide management to either prevent or minimize the effects. Continuous monitoring of blood pressure is essential and vigorous efforts should be maintained to control it, preferably below 160/90 mm Hg. Elimination of bladder infection and bowel impaction is important in decreasing the nociceptive stimuli from the pelvic viscera and thus reducing the risk of crisis. It should be remembered that such a simple manipulation as a catheter change may provoke autonomic hyperreflexia. Topical anesthesia of the urethral, rectal, and vesical mucosa is usually sufficient to avoid such an episode.[2] Ganglionic blocking drugs such as hexamethonium and guanethidine have been found to be helpful in suppressing the autonomic hyperreflexia.[19, 20] Low spinal or epidural anesthesia is generally sufficient to block the impulses from pelvic structures and to prevent their occurrence entirely.[2] The continued autonomic hyperreflexia after the injection of epidural anesthesia in this patient was perhaps due to the technical difficulty encountered. Cesarean section in a spinal cord–injured woman is not mandatory; rather, a normal delivery should be expected.[13, 16] Seventeen patients in our institution have now been delivered at term over the past 8 years. In these only two cesarean sections were done; the other was necessitated by an obstetrical complication (bleeding). However, if autonomic hyperreflexia becomes acute during labor and cannot be controlled, prompt delivery by cesarean section is the most expedient method of management.

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Cesarean hysterectomy: A twenty-five–year review

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This article analyzes cesarean hysterectomies performed at Louisville General Hospital on clinic patients for the 25 year period 1953 through 1977. During this time there were 63,259 deliveries, of which 2417 were cesarean sections and 149 were cesarean hysterectomies. Twenty-six of the latter were classified as emergency operations done for urgent medical indications; in the remaining 123 patients the indications were elective to some degree. Operative and postoperative complications and morbidity are discussed, and changing trends regarding the place of cesarean hysterectomy in obstetrics over the years are evaluated. (AM. J. OBSTET. GYNECOL. 134:393, 1979.)

IT WAS IN 1876 that Porro[1] proposed a method for amputating the recently gravid uterus immediately after delivery by cesarean section in order to reduce the considerable death rate from the classical form of that operation. Since Porro's time, elective hysterectomy at the time of cesarean section has been a controversial procedure in obstetrics.

When cesarean hysterectomy is performed on an elective rather than an emergency indication, it has been denounced by many authors on the grounds that it is an unduly radical operation, particularly as regards blood loss. On the other hand, there have been some proponents of the viewpoint that cesarean hysterectomy can be an acceptable method for sterilization under certain circumstances. In a classic paper, Prystowsky and Eastman[2] concluded that the hazards of all sterilization procedures in grand multiparas were far less than those imposed by further pregnancy episodes. Haynes and Wolfe[3] reported a 2% failure rate of tubal ligation; 36% of the medically indigent patients in their series required gynecologic operations later on.

Significant recent reports on this subject are those of Barclay and associates[4] and O'Leary.[5] Review of the English language literature since 1953, excluding articles reporting fewer than 30 cesarean hysterectomies, indicates that: (1) From 1953 to 1977, there were 2,844 elective and 1,519 indicated cesarean hysterectomies reported, with a maternal mortality rate of 0.6%[8–26]; (2) Barclay has had more experience with this procedure than any other author[4]; (3) the subject was extensively debated in the latter half of the 1960's; (4) there is a significant though debatably acceptable low maternal mortality rate associated with the operation.

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Material and methods

This report reviews 149 cesarean hysterectomies performed at Louisville General Hospital from 1953 through 1977. During those years there were 63,259 deliveries, of which 2,417 were cesarean sections (3%). Of these cesarean sections, 149 were cesarean hysterectomies (6.2% of the cesarean sections or 0.23% of all the deliveries).

In this series, each cesarean hysterectomy was classified as either an elective or an indicated procedure. *Elective* operations were performed for purposes other than immediate salvage of life, e.g., sterilization, functional uterine disorders, and myomas (see Table I). *Indicated* operations were those performed primarily as life-saving procedures in such acute emergencies as ruptured uterus with massive bleeding, amnionitis, and severe abruptio placentae (see Table II). Of the 123 "elective" cesarean hysterectomies, 119 were total hysterectomies and 2 were subtotal. Twenty-six "indicated" operations were performed; of these, all were total hysterectomies except for two subtotal operations.

The average parity of the patients in the "elective" category was 3; in the "indicated" category it was 4.

With respect to age, in the "elective" series the youngest patient was 18 years of age and the oldest was 41, with an average age of 29. In the "indicated" series,

Table I. Indications in 123 elective cases

	No.
Previous section (s)	
And multiparity or request for sterilization	100
And hypertension	4
And fetal death *in utero*	2
And myomata	3
And uterine prolapse	1
Hypertension, diabetes, myomas, and Rh immunization	10
CPD, malpresentation and mental deficiency	3

Table II. Indications in 26 indicated cases

	No.
Amnionitis	9
Ruptured uterus	6
Impending uterine rupture	2
Failed induction of obligation	1
Severe abruptio placentae (Couvelaire uterus and dysplasia)	3
Long-ruptured membranes, inertia, myomas, low implantation of placenta	1
Coagulopathy	2
Carcinoma in situ of cervix	1
Old uterine perforation with defect	1

Table III. Complications and morbidity

	No.
Anemia without fever	15
Cuff cellulitis or abscess	11
Iatrogenic cystotomy	10
Urinary tract infections	9
Atelectasis	7
Wound infections	6
Pneumonia	5
Ileus	4
Pelvic abscess	4
Broad ligament hematoma	4
Pulmonary embolus	2
Pyelonephritis	2
Laryngeal edema	1
Parametritis	1
Wound dehiscence with evisceration	1
Internal iliac vein laceration	1
Intestinal obstruction	1
Rectovaginal fistula	1
Ureterovaginal fistula	1
Hemoperitoneum	1

the youngest patient was 25 and the oldest was 44, the average age being 32.

Among the 26 "indicated" operations, amnionitis was the most common indication (nine cases), with uterine rupture the next in frequency (six cases). Among the 123 "elective" operations, multiparity or request for sterilization by patients who had been delivered by cesarean section in one or more previous pregnancies were the most prevalent indications.

The majority of the 149 operations were performed under general anesthesia, with spinal anesthesia next in frequency.

Of the 149 cesarean hysterectomies, 132 were performed by the senior resident in training as principal operator under staff supervision. The remaining 15 operations were carried out by a member of the attending staff as principal operator.

Results and comment

Some critics of cesarean hysterectomy have emphasized that it is a lengthy operation, entailing excessive operative morbidity as compared with cesarean section and tubal ligation.

In the 149 cesarean hysterectomies of this series, the average operating time was 132 minutes. The longest time required was 417 minutes and the shortest operating time was 42 minutes.

The patient requiring the shortest operating time was a 40-year-old woman, gravida 15, para 14, who had premature rupture of the membranes and failed induction of labor. Ironically, hers was the only postoperative death in the series; she died following a massive pulmonary embolus on the third postoperative day.

The patient with the longest operating time was a 37-year-old woman, gravida 4, para 3, with a complete placenta previa, who had undergone two previous cesarean sections. The operation was complicated by an intraoperative accidental laceration of the right internal iliac vein. The resulting hemorrhage was ultimately controlled, but necessitated 11 units of blood replacement. The combination of the central placenta previa and the iliac vein laceration occasioned the inordinately long operating time in this patient, who, incidentally, was operated on by an attending staff member rather than a resident as principal surgeon.

This case calls to mind a commonly cited disadvantage of cesarean hysterectomy, namely, the excessive blood loss reported with the procedure. Certainly the operation is attended by a more formidable blood loss than is abdominal hysterectomy in the nonpregnant woman. However, in this series, 32 of the patients required no transfusion of blood and 40 others received only one unit each, suggesting that transfusion was superfluous in those instances. Eleven patients required 5 or more units of blood; 10 of these patients had either severe abruptio placentae or placenta previa. All 11 were complicated by coagulopathy. One patient received 21 units of blood replacement. She was a 29-year-old woman, gravida 7, at 36 weeks' gestation, who had sustained extensive blunt trauma to the abdomen involving a laceration of the liver which required ligation of the right and medial segmental hepatic arteries.

Cesarean section was done because of evidence of fetal distress, and post-section hemorrhage secondary to coagulopathy made hysterectomy mandatory. The patient ultimately recovered.

Ancillary operations at the time of cesarean hysterectomy in the series reported included 19 incidental appendectomies, 15 salpingo-oophorectomies, and 10 repairs of iatrogenic cystotomy incisions.

Complications and morbidity encountered in this series of patients undergoing cesarean hysterectomy are summarized in Table III. In consonance with most published reports was the occurrence of 10 instances of bladder injury, which thus constituted the most common operative complication. Postoperative cuff cellulitis or abscess, observed in 11 patients, was the most frequent cause of febrile morbidity. Four patients developed broad-ligament hematomas; two of these required unilateral salpingo-oophorectomy and one hypogastric artery ligation.

Postoperative febrile morbidity occurred in 51 patients. There were 15 patients with postoperative anemia unassociated with febrile episodes. Two patients suffered pulmonary emboli, one of which accounted for the only maternal death.

The average hospital stay per patient was 9 days, or about 2 days longer than that of most patients undergoing abdominal hysterectomy and 4 days longer than the average for cesarean section. The longest stay was 21 days and the shortest was 4 days.

With regard to fetal outcome, 13 of the 149 infants were stillborn (8.8%); the other 136 infants were healthy and survived. Clinical circumstances associated with the 13 stillbirths included three instances of amnionitis, three ruptured uteri, and three cases of abruptio placentae. There were two unexplained deaths in utero, one secondary to an umbilical cord wrapped four times around the neck and one death in an anencephalic infant.

Follow-up studies on the 149 patients treated by cesarean hysterectomy showed that 36 of the patients were lost to follow-up. Seventy-six patients were known to have been living and well for up to 1 year following operation. Fifteen patients were alive more than 1 year later, with unrelated illnesses. Two of the latter had hypertensive cardiovascular disease. One patient who had a diagnosed ureterovaginal fistula refused reparative operation. Another patient who developed a rectovaginal fistula had a successful repair 2 years later.

In reviewing the data from this series, it is noteworthy that during the period 1962 to 1970 there was a striking increase in the number of cesarean hysterectomies performed at Louisville General Hospital as compared with previous years, whereas in subsequent

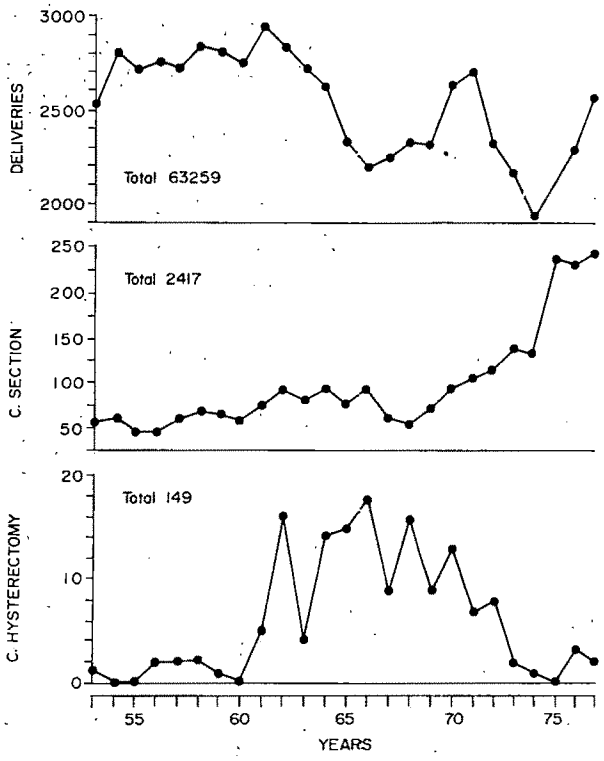


Fig. 1. Cesarean hysterectomies at Louisville General Hospital, 1953 to 1977.

years the operation was performed with greatly diminished frequency. Fig. 1 illustrates the distribution of cesarean hysterectomies during the years in question. The trends illustrated resulted from the adoption in 1962 of a liberalized attitude toward elective as opposed to emergency indications for the procedure, reflecting the nationwide interest in re-evaluating this point at that time. It was thought that it might be worthwhile to document the results that could be obtained in a single institution in which most of the operations would be performed by residents in training under appropriate staff supervision to test the point, so frequently made in the pertinent literature, that a key feature of satisfactory outcome in elective cesarean hysterectomy is the experience of the operator. It should, of course, be understood that resident education per se was in no way the underlying motivation for liberalizing the indications for the operation.

The dramatic decrease in the number of cesarean hysterectomies since 1970 reflects changes in departmental policy resulting in part from accumulated experience and in part from changing philosophy with regard to the elective performance of the operation.

From operative experiences and postoperative sequelae a few general conclusions seem warranted regarding the liberal use of "elective" cesarean hysterec-

tomy. The operation is greatly complicated by the presence of a complete placenta previa. There should be in each case an acceptable obstetric indication for abdominal delivery. Blood loss is not invariably excessive, nor is operating time necessarily greatly prolonged in the average case. Occasionally it may be justifiable to perform the subtotal rather than the total operation, but this modification is probably more appropriate in complicated emergency situations than it would be in less urgent circumstances. Operative and postoperative morbidity is a significant consideration.

In conclusion, while cesarean hysterectomy should remain in the obstetrician's repertoire for use in appropriate situations, our experience suggests that it may be relatively inadvisable to employ this procedure for strictly elective indications.

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Discussion

DR. CLARENCE F. WEBB, Grand Rapids, Michigan. Many years ago, Dr. Ralph Reis discussed the problem of comparing elective and indicated cases of cesarean hysterectomies as similar to that of comparing apples and oranges. Unfortunately, this problem exists in most of the papers that are presented on cesarean hysterectomy, as it is hard to assemble a series large enough to become significant for either group.

Dr. Haynes is correct in saying that they have deemphasized the procedure at a time when cesarean section is increasing. They have tripled their cesarean section rate. It might be assumed that the number of cesarean hysterectomies would increase; however, they performed only 10 in the last 5 years. It is assumed that, in a teaching service with this low volume, there would be no residents being trained in more than a casual familiarity with the procedure. I wonder if this indicates a trend that, in the future, will be comparable to some residents' training in delivering a primigravida with breech presentation.

The authors quote Prystowsky and Eastman as saying that the hazards of sterilization procedure were less than those imposed by pregnancy. Actually, those authors concluded that grand multiparity did not constitute a true medical indication for sterilization. The Johns Hopkins University had previously published a report advocating tubal ligation for grand multiparity. However, the paper quoted had been written to refute this earlier report because of the high failure rate and the ectopic pregnancies that occurred after a tubal li-

gation. This made it a rather unprecedented article, reversing an earlier position.

I still feel that there are valid reasons to do an elective cesarean hysterectomy in preference to a tubal ligation at the time of a repeat cesarean section.[1] The ideal patient is not obese and has a hemoglobin of 12 gm or more. The main advantages to the patient are that she is assured of sterilization and further uterine disease is markedly decreased. Therefore, any risk of future surgical procedures is decreased in the patient. Each patient, however, has to be individually considered before a choice of procedure is made. In private practice, the patients that have cesarean hysterectomy are well satisfied with the end results.

The procedure should be comparable to an abdominal hysterectomy in ideal circumstances. It is the combination of the cesarean section alone, such as bladder injury, plus the obstetric complications, that tends to make the obstetric operator become concerned about performing a cesarean hysterectomy. Barclay's large series has indicated that in an institution similar to Louisville, where primarily residents are doing the surgery, it is possible for residents to gain adequate experience, so that morbidity rates can be reduced and transfusions decreased to acceptable minimums. Then, faced with an obstetric emergency, a resident can safely accomplish a cesarean hysterectomy.

It is noted that four of the patients in Dr. Haynes' series had a subtotal hysterectomy. This is one situation in which residents in training might do well to do a few subtotal hysterectomies to familiarize themselves with the technique as a teaching mechanism. However, the patient must be continually followed and the cervix observed. Follow-up may be a problem in some cases.

REFERENCE

1. Webb, C. F., and Gibbs, J. V.: Cesarean Hysterectomy, Gynecology and Obstetrics, Hagerstown, Md., 1978, Harper & Row, vol. 2, chap. 85.

DR. SAM P. PATTERSON, Memphis, Tennessee. Cesarean hysterectomy was once my favorite operation, when I was a resident and subsequently on the full-time faculty. I also had the privilege of presenting a paper on the subject to this association in 1969. At that time, I reviewed 327 cesarean hysterectomies performed over a 14 year period at the University of Tennessee in Memphis. Its popularity has waned there also, not only because of its morbidity rate but also probably because elective sterilization is now so frequently performed for young women. Most authors have agreed that its associated morbidity rate is a deterrent to elective cesarean hysterectomy. The complications reported by Dr. Haynes are similar to those of others. He reports, however, a rather high incidence of iatrogenic cystotomy, 10 in 149 cesarean hysterectomies, whereas we had only three in 327 cases, nearly all of which also were performed by residents. Dr. Haynes' classification of repair of iatrogenic cystotomy as an ancillary operation such as appendectomy is a new designation. He may also have a "first" with the reported rectovaginal fistula. I should like to ask how this occurred.

Dr. Haynes mentioned four subtotal hysterectomies. Since nearly all bladder injuries occur in patients who have had previous cesarean section, I continue to suggest that subtotal hysterectomy is frequently better than total hysterectomy if there is the slightest difficulty in advancing the bladder. Adherence of the bladder to the cervix after previous low cervical cesarean section allows easy perforation. I should like to ask Dr. Haynes if any of his subtotal operations were done because of previous cesarean section. I also suggest that varicosities beneath the bladder are a contraindication to total cesarean hysterectomy. The bladder must be advanced with extreme gentleness, and for this operation I suggest using a moist gloved finger rather than scissors that cut vessels or rough sponges that tear veins. In addition, this operation should be performed only by obstetricians with surgical assistants who are all clearly aware of the tremendous vascularity of the puerperal pelvis.

Dr. Haynes has reported four broad ligament hematomas, emphasizing the frequency of this complication. Venous plexi in the pelvis are extremely large and easily torn in the multipara at term. The broad ligament must be handled very gently.

Dr. Webb has lauded the simplicity of cesarean hysterectomy and its paucity of complications, saying that cesarean hysterectomy is preferable to cesarean section and tubal ligation. I wonder what his thoughts are about the morbidity in this series, especially the two fistulas. I hasten to say that both his and my series included one urinary tract fistula each. The mortality rate reported by most authors emphasizes that there must be an obstetric indication for cesarean section before cesarean hysterectomy is contemplated, unless it is done for preinvasive cancer of the cervix. If cesarean hysterectomy is decided, then total or subtotal must be considered, since nearly all urinary tract injuries occur with total hysterectomy. There should be no embarrassment for subtotal cesarean hysterectomy, the opinion of Blue Cross notwithstanding. The risk of total cesarean hysterectomy may not always be justified. Lastly, I would comment that a comparison of morbidity might be more appropriately made with cesarean section rather than simple total abdominal hysterectomy.

DR. THOMAS W. MCELIN, Evanston, Illinois. To debate with a classicist such as Douglas Haynes is indeed treading in very deep water. However, I think it is time that the name of Dr. Porro in primary association with this operation should be put aside.

Irving,[1] in his charming book entitled *Safe Deliverance,* makes it very clear that the operation was first performed by Horatio R. Storer of Boston approxi-

mately 8 years (1868) before Dr. Porro. Perhaps, because the name of Dr. Eduardo Porro of Milan has been so long associated with cesarean hysterectomy, the eponym of the Storer-Porro operation might be substituted for the Porro eponym.

REFERENCE

1. Irving, F. C.: Safe Deliverance, Boston, 1942, Houghton Mifflin Company.

DR. BROOKS RANNEY, Yankton, South Dakota. The point has been made several times that there is an increased morbidity rate in association with cesarean hysterectomy. However, we have observed factors relating to a cesarean hysterectomy that also decrease the morbidity rate. These result from the removal of the uterus and the placental site.

Removal of a grossly infected uterus, a severely hemorrhaging uterus, or one containing large, degenerating myomas will be of immediate benefit to the patient. Postoperative ileus is less following cesarean hysterectomy than it is after cesarean section. A patient with pregnancy toxemia recuperates more rapidly after removal of the uterus. Cesarean hysterectomy eliminates the phenomenon of involution of the decidua and myometrium, which would otherwise cause fever and an abnormally elevated blood urea nitrogen by the third and fourth postpartum days.

In our hands most patients feel better and heal better, sooner, following cesarean hysterectomy, than they would following cesarean section, despite the unusual obstetric complications which produced the rare indications for cesarean hysterectomy.

DR. JOSEPH A. LUCCI, JR., Houston, Texas. Reference has been made to the technical difficulties which cause the blood loss and broad ligament hematomas.

I think one factor which predisposes to blood loss in a patient who has been in labor is the difficulty of identifying where the cervix ends and the vagina begins. Such patients can present a difficult technical surgical problem which may predispose to additional bleeding or hematoma formation.

DR. HAYNES (Closing). Dr. Webb, the reason for the policy change that resulted in a great diminution of the number of cesarean hysterectomies in our series was not only a change in policy but also a change in department chairmen, and a consequent change in philosophy which was reflected in other institutions as well.

During the years that we did this operation more or less electively I had hoped to continue the trend of liberalized indications as long as it seemed to be feasible from the point of view of safety of the patients. Indeed, during those years, I think we did have as a serendipity an excellent training program for residents to learn the procedure. The diminishing incidence of cesarean hysterectomies was not confined to our institution, but reflected a national trend that still continues.

Dr. Patterson questioned the classification of iatrogenic cystotomy as an ancillary operation. This is merely a matter of semantics. We expected a certain amount of bladder injury because of the nature of the procedure. I will note that there were no serious sequelae of the iatrogenic cystotomies in our series. Our one ureterovaginal fistula was not associated with recognized bladder injury.

Dr. Patterson asked how we happened to get a rectovaginal fistula. This was a surprise to us also. In that particular patient we were not conscious of having encountered any problems around the rectum, but the patient did end up with a rectovaginal fistula which we had to repair.

As far as the subtotal operations are concerned, I agree that there should be no absolute rule that a subtotal operation is never to be performed under any circumstances. Two of our subtotal operations were done in emergency situations in which a great deal of hemorrhage and a great deal of trauma were present, and we wanted to get the operation done as quickly as possible. Two of them had extensive adhesions and scar tissue formation because of previous cesarean sections, and it was thought at the time by the staff member in attendance at the operation that it would probably be safer in that situation to do a subtotal operation.

Dr. McElin rightly puts me in my place about Eduardo Porro. However, Prof. Porro's classic description of the *taglio cesareo demolitore* was the one that popularized the procedure in the world literature. I did not mean to imply that Porro was necessarily the first to perform it, but he appears to have been the first to publicize it so that it became a well-known procedure.

I appreciated Dr. Ranney's remarks, and also those of Dr. Lucci, who suggested that perhaps complications are more likely if this operation is done prior to the formation of a well-defined, thinned-out lower uterine segment. This has been our experience also. On the other hand, I feel that sometimes it would not be particularly desirable, particularly in cases of previous cesarean section, to await thinning of the lower uterine segment in view of the risk of uterine rupture.

A controlled trial of the differential effects of intrapartum fetal monitoring

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A controlled prospective study of the differential effects of intrapartum fetal monitoring on mothers and infants has been conducted at Denver General Hospital, Denver, Colorado. A total of 690 high-risk obstetric patients in labor were randomly assigned to one of three monitoring groups—auscultation, electronic fetal monitoring alone, or electronic monitoring with the option to scalp sample. There were no differences in immediate infant outcomes in any measured category (Apgar scores, cord blood gases, neonatal death, neonatal morbidity, nursery course) among the three groups. There were no differences in rates of infant or maternal infections. The cesarean section rate was markedly increased in the electronically monitored groups, especially in the electronically monitored alone (18%) as compared with the auscultated (6%) ($P < 0.005$). In this controlled trial electronic monitoring did not improve neonatal outcomes and the mothers were at increased risk of cesarean section. (AM. J. OBSTET. GYNECOL. 134:399, 1979.)

DURING THE PAST DECADE, intrapartum electronic fetal monitoring has become increasingly widespread in clinical obstetrics[1–5] and is thought to improve perinatal outcome, especially among high-risk obstetric patients.[6–13] This paper reports an effort to assess clinical effectiveness of three methods of clinical intrapartum fetal monitoring presently used in this country: auscultation, electronic fetal heart rate monitoring, and electronic fetal heart rate monitoring combined with fetal scalp sampling. A randomized prospective clinical trial was used to evaluate these techniques.

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A previous study, from 1973 to 1975, at Denver General Hospital in Denver, Colorado, examined the effects of electronic fetal heart rate monitoring and careful auscultation on a group of 483 high-risk patients.[14] There were no significant differences in infant outcomes between the monitored and auscultated groups. The results of this study were contrary to our expectations. A new study was begun in July, 1975, with a similar study design which included additional measures of infant status at birth and at 9 months of age.

Study design

The specific objectives of the new study were to assess, by means of a randomized controlled trial, the differential effects of continuous electronic monitoring and fetal pH scalp sampling on high-risk mothers and their offspring, as compared with outcomes among auscultated mothers. The basic question asked by this research is whether or not electronic monitoring significantly improves a variety of outcomes for mothers and infants.

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Table I. Marital status of mothers

	Aus (N = 226)	*EM (N = 220)*	*EM + SS (N = 223)*	*Total (N = 669*)*
Married	106 (47%)	117 (53%)	104 (47%)	327 (49%)
Single	78 (34%)	79 (36%)	87 (39%)	244 (36%)
Divorced, separated, widowed	35 (16%)	21 (10%)	26 (12%)	82 (12%)
Common-law	7 (3%)	3 (1%)	6 (3%)	16 (2%)
	100%	100%	101%	99%

*Twenty-one mothers did not respond to this question. p = 0.35 (NS).

Table II. Mother's age

	Aus (N = 231)	*EM (N = 230)*	*EM + SS (N = 229)*	*Total (N = 690)*
≤16	29 (13%)	26 (11%)	26 (11%)	81 (12%)
17-30	183 (79%)	187 (81%)	185 (81%)	555 (80%)
>30	19 (8%)	17 (7%)	18 (8%)	54 (8%)
	100%	99%	100%	100%

p = 0.99 (NS).

Method

The obstetric part of the study ran from July, 1975, to July, 1977, and consisted of a group of 690 high-risk mothers in labor. There were five sets of twins so the total number of infants was 695.

Mothers were admitted to the study either on the basis of their over-all risk status and/or if they developed certain labor abnormalities that most authorities consider high risk per se. Assignment of risk was based on a system developed by Goodwin, Dunne, and Thomas.[15] Two points could be subtracted in any of five categories: past medical history, past obstetric history, current prenatal course, present labor evaluation, and estimated gestational age. A low-risk patient would have no points subtracted and thus have a score of 10. Patients with scores of 6 or less were considered high risk. Women were also admitted to the study if they had meconium-stained amniotic fluid, abnormal fetal heart tones by auscultation, an arrested labor, or significant pre-eclampsia, or if they required oxytocin. Because of the difficulties in evaluating neonatal outcomes between markedly premature and term infants, mothers whose fetuses were estimated to be less than 34 weeks' gestational age or less than 2,000 grams were not admitted to the study.

When a mother was determined to be high risk she was, with her consent, randomly assigned to one of three fetal monitoring groups: auscultation alone (Aus), electronic monitoring alone (EM), or electronic monitoring with option to obtain fetal scalp pH (EM + SS). All the patients were allotted a sealed envelope to remove any antenatal bias. This envelope contained a slip of paper marked A for auscultation, B for electronic monitoring alone, and C for electronic monitoring with option to scalp sample. The EM groups had internal monitoring (Hewlett Packard Cardiotocograph)—(scalp electrode and pressure catheter) applied as soon as this was feasible during labor. Until such time, the patients were followed by external monitoring with an ultrasonic transducer and a tocodynamometer.

All mothers were attended by individual study nurses who insured that the quality of care and the time spent with the patient were the same in each study group. The study nurses notified the labor area doctor and the staff doctor as to abnormalities of fetal heart rate for both auscultated and electronically monitored patients. Final decisions regarding cesarean sections were made by the staff physicians.

The Aus group of patients had fetal heart tones auscultated and recorded 30 seconds after a contraction at least every 15 minutes in the first stage of labor and every 5 minutes in the second stage. Fetal distress (or ominous fetal heart rates) was defined in this auscultated group as fetal heart tones of less than 100 bpm after three or more consecutive contractions despite such corrective measures as changes in position, oxygen administration, correction of hypotension, etc. Such patients were delivered as quickly as possible. "Nonreassuring" fetal heart rates included fetal tachycardia, bradycardia between 100 and 120 bpm, and irregular heart rate.

In the Em group, fetal distress ("ominous" patterns) was defined as late decelerations, severe variable decelerations, tachycardia with total loss of short-term variability, or marked bradycardia that was not relieved by corrective measures within 15 to 30 minutes. Such patients were delivered immediately. Fetal heart rate patterns that were "nonreassuring" but not "ominous," as the preceding, included tachycardia with good variability, moderate bradycardia, diminished and absent short-term variability with a normal baseline, moderate variable decelerations, variable decelerations with late return to baseline, or patterns that were difficult to interpret. Patients with nonreassuring tracings were allowed to continue labor unless there were other clinical indications for its termination. The criteria developed by Kubli and associates[16] were employed to evaluate the decelerations. All tracings were reviewed at the con-

Table III. Racial background of mothers

	Aus (N = 219)	*EM (N = 223)*	*EM + SS (N = 226)*	*Total (N = 668*)*
Caucasian	83 (38%)	83 (37%)	71 (31%)	237 (35%)
Spanish-American	113 (52%)	102 (46%)	114 (50%)	329 (49%)
Black	23 (10%)	38 (17%)	41 (18%)	102 (15%)
	100%	100%	99%	99%

p = 0.12 (NS).
*668 mothers provided this information.

Table IV. Education level achieved by mothers

	Aus (N = 210)	*EM (N = 197)*	*EM + SS (N = 200)*	*Total (N = 607*)*
Some college or higher	14 (7%)	24 (12%)	18 (9%)	56 (9%)
High school graduate	60 (29%)	52 (26%)	57 (28%)	169 (28%)
Partial high school	86 (41%)	87 (44%)	89 (44%)	262 (43%)
Junior high or less	50 (24%)	34 (17%)	36 (18%)	120 (20%)
	101%	99%	99%	100%

*607 mothers provided this information. p = 0.36 (NS).

Table V. Occupation of head of household in which mothers reside

	Aus (N = 167)	*EM (N = 166)*	*EM + SS (N = 166)*	*Total (N = 499*)*
Executives, small business owners, semiprofessionals	6 (3%)	4 (2%)	7 (4%)	17 (3%)
Skilled and semiskilled workers	74 (44%)	80 (48%)	64 (39%)	218 (44%)
Unskilled workers	87 (52%)	82 (49%)	95 (57%)	264 (53%)
	99%	99%	100%	100%

*499 mothers provided this information. p = 0.46 (NS).

clusion of the study by an outside independent reviewer.

The infants of mothers in the EM + SS group were scalp sampled after 3 to 4 cm cervical dilatation had been reached when patterns were ominous or nonreassuring. A maternal venous sample was also obtained. A pH value of 7.20 to 7.25 was considered problematic and that of less than 7.20 was considered to be a sign of acidosis and an indication for immediate action if this value was at least 0.15 units less than that of the mother. Determinations were repeated every 20 minutes if the fetal heart rate pattern continued to be ominous or nonreassuring.

Infant outcomes were measured by Apgar scores at 1 and 5 minutes, cord blood gases at birth, Brazelton neonatal assessment at 2 to 3 days, neonatal death, neonatal morbidity (incidence of seizures, etc.), comprehensive pediatric physical examination at 9 months, and infant neurologic development as measured by the Bayley and Milani-Comparetti tests at 9 months of age. The last two, as mentioned, are not yet complete and, together with the Brazelton assessments, will be the subject of another report.

Results

Analysis of data. The data were computerized and analyzed by the Biometrics Department of the University of Colorado Medical Center. Chi-square analyses and analysis of variance were used where appropriate. The p values presented in the accompanying tables were determined by chi-square discrete (count) data and one-way analysis of variance for continuous (mean and S.E.M.) data.

Mothers' sociodemographic characteristics. The study population might be characterized as being at higher socioeconomic risk than one would find in most communities, but it is typical of that cared for by many city-county hospitals. Almost all mothers came from households where the heads were semi- or unskilled laborers. More than one third were single. Many were from minority backgrounds, with close to half of the total being Spanish-American. Relevant to this investigation, there were no significant differences among the three study groups with respect to maternal age, race, marital status, educational level achieved, or occupation of head of household (Tables I to V).

Risk status of mothers. The risk system used to admit mothers to the study guaranteed the appropriateness of their entry, but not that the major categories of risk would have similar distributions within the three study groups. With respect to over-all risk criteria upon entrance to the study (Table VI), somewhat over half of all patients were admitted to the study because of a score of 6 or less, 37% because of disturbing events

Table VI. Reasons for entry into study

	Aus (N = 231)	*EM (N = 230)*	*EM + SS (N = 229)*	*Total (N = 690)*
High-risk score alone	128 (55%)	127 (55%)	101 (44%)	356 (52%)
High-risk score + other factors	26 (11%)	21 (9%)	29 (13%)	76 (11%)
Abnormal fetal heart tones	3 (1%)	7 (3%)	3 (1%)	13 (2%)
Meconium alone	25 (11%)	31 (13%)	45 (20%)	101 (15%)
Oxytocin alone	33 (14%)	31 (13%)	31 (13%)	95 (14%)
Pre-eclampsia alone	7 (3%)	2 (1%)	4 (2%)	13 (2%)
Arrested labor alone	9 (4%)	11 (5%)	16 (7%)	36 (5%)
	99%	99%	100%	101%

p = 0.08 (NS).

Table VII. Maternal and infant clinical status—mean scores + S.E.M.*

	Aus	*EM*	*EM + SS*	*p value*
Maternal age	21.8 ± 0.33	22.2 ± 0.35	21.9 ± 0.34	0.77 (NS)
Gravidity	2.34 ± 0.11	2.28 ± 0.11	2.20 ± 0.11	0.69 (NS)
Parity	0.96 ± 0.09	0.87 ± 0.08	0.90 ± 0.09	0.77 (NS)
Risk score	6.10 ± 0.10	5.97 ± 0.12	6.25 ± 0.11	0.20 (NS)
Weeks' gestation	39.7 ± 0.10	39.8 ± 0.12	39.7 ± 0.11	0.93 (NS)
Birth weight	3,130 ± 33.3	3,183 ± 35.2	3,089 ± 33.1	0.14 (NS)

*Standard error of the mean.

Table VIII. Distribution of gestational age categories

	Aus (N = 232)	*EM (N = 233)*	*EM + SS (N = 230)*	*Total (N = 695)*
Preterm (34-37 weeks):	19 (8%)	24 (10%)	24 (10%)	67 (10%)
LGA*	0	1	0	
AGA	16	18	21	
SGA	3	5	3	
Term (38-42 weeks):	206 (89%)	196 (84%)	193 (84%)	595 (86%)
LGA	23	26	23	
AGA	171	161	159	
SGA	12	9	11	
Postterm (42 weeks):	7 (3%)	13 (5%)	13 (6%)	33 (5%)
LGA	0	1	1	
AGA	7	11	12	
SGA	0	1	0	
				101%

*LGA = Large for gestational age; AGA = appropriate for gestational age; SGA = small for gestational age. p = 0.5 (NS) This value refers to the major categories: preterm, term, and postterm.

during labor, and the remaining 11% because they had both a score of 6 or less as well as high-risk factors uncovered during labor. There was no significant difference in the distribution of these among the three groups.

A summary of a number of maternal and infant characteristics, which are known to be important clinical determinants of infant outcome, is presented in Table VII. There were no significant differences among the three study groups in the means of maternal age, parity, over-all risk score on admission to the study, weeks' gestation, or birth weight.

Gestational ages of the infants at birth and whether they were average, small, or large for gestational age are shown in Table VIII. Most were average for gestational age. These did not differ significantly among the three groups.

As mentioned, certain abnormal developments encountered during labor were tabulated (Table IX). Pre-eclampsia was further subdivided into mild and severe cases according to the method of Pritchard and MacDonald.[23] The distribution of arrested labors requiring oxytocin, presence of meconium, presence of pre-eclampsia, and the development of amnionitis among the study groups was not significantly different.

Outcomes. Fetal heart rate patterns and their distributions are displayed in Tables XA, XB, and XC. Because of the capacity of the electronic monitor to identify certain patterns (i.e., variability, late decelerations) with far greater accuracy than is possible by ausculta-

Table IX. Characteristics during labor

	Aus	*EM*	*EM + SS*	*p value*
Required oxytocin augmentation	64	63	76	0.29 (NS)
Meconium	72	85	80	0.39 (NS)
Pre-eclampsia, mild	7	8	7	0.08 (NS)
Pre-eclampsia, severe	37	28	17	
Amnionitis	1	0	2	—

tion, "reassuring" patterns are reported more frequently in the auscultated group. The distribution of various electronically monitored patterns is presented in Table XI. Independent obstetric review of these patterns was in agreement 90% of the time. In the electronic monitoring plus scalp sample group, scalp pH sampling was done on 44 patients.

Routes of delivery are presented in Table XII and modes of delivery in Table XIII. Here, monitored alone patients had a significantly higher cesarean section rate than did auscultated patients (18% vs. 6%). This applied to both the number of cesarean sections done for fetal distress as well as to sections done for other reasons, of which cephalopelvic disproportion or failure to progress were the most common indications. This incidence was lower in those mothers in whom scalp sampling was optional but the difference is not significant. There was also no significant difference in the total number of cesarean sections among electronically monitored patients with option to scalp sample and among auscultated patients. The use of general anesthesia was also higher in both of the monitored groups (Table XIV). This reflected the higher incidence of cesarean section in these patients.

Tables XVA and XVB present two types of data: the administration of antibiotics and the presence or absence of infection. The latter data are more appropriately regarded as outcomes in that they reflect maternal morbidity following delivery. Table XVA presents the rates of postpartum infections in vaginal deliveries. There were no differences in postpartum infections among the three groups. Table XVB gives the rates of infection among the three groups when cesarean sections were done. There were no differences. At Denver General Hospital, prophylactic antibiotics are routinely given to patients in labor undergoing cesarean sections.

There were excellent perinatal outcomes in all groups, with no intrapartum deaths and three neonatal deaths, none of which was related to monitoring techniques. Of these three neonatal deaths, two were in the EM group and one was in the EM + SS group. In the EM group, one infant died at birth from a massive intracranial hemorrhage which was found at autopsy to have occurred prior to the onset of fetal monitoring. The second infant died 30 hours after repair of a diaphragmatic hernia. The infant in the EM + SS group had an uneventful nursery course, was discharged from the hospital at 3 days of age, and died at age 3 weeks from overwhelming sepsis. The perinatal mortality rate was 4.3 per thousand.

Table XA. Fetal heart rate patterns during early first stage of labor

	Aus (N = 160)	*EM (N = 157)*	*EM + SS (N = 140)*
Reassuring	152 (95%)	134 (85%)	109 (78%)
Nonreassuring	8 (5%)	8 (5%)	18 (13%)
Ominous	0	15 (10%)	13 (9%)
	100%	100%	100%

$p < 0.005$ (sig). Early first stage of labor ≤5 cm.

Table XB. Fetal heart rate patterns during late first stage of labor

	Aus (N = 221)	*EM (N = 226)*	*EM + SS (N = 219)*
Reassuring	204 (92%)	183 (81%)	172 (78%)
Nonreassuring	16 (7%)	35 (15%)	38 (17%)
Ominous	1	8 (3%)	9 (4%)
	99%	99%	99%

$p < 0.005$ (sig). Late first stage of labor >5 cm.

Table XC. Fetal heart rate patterns during second stage of labor

	Aus (N = 207)	*EM (N = 162)*	*EM + SS (N = 171)*
Reassuring	185 (89%)	123 (76%)	110 (64%)
Nonreassuring	18 (9%)	30 (18%)	50 (29%)
Ominous	4 (2%)	9 (5%)	11 (6%)
	100%	99%	99%

$p < 0.005$ (sig). Second stage = complete dilation to delivery.

The condition of the infants following delivery was appraised at 1 and 5 minutes by means of the Apgar method. Mean scores are presented in Table XVI, showing no differences, nor were there significant differences in the distribution of scores (Table XVII).

The biochemical status of the infants at birth was assessed. Venous and arterial cord blood pH values were analyzed since they are indicators of intrauterine hypoxia and fetal acidosis. There were no differences in the mean pH and blood gas values in the three groups (Table XVIII) except for the venous Pco_2. A venous pH of 7.25 or less and an arterial pH of ≤7.20 or less were considered to be problematic. There were

Table XI. Fetal monitor pattern distribution

	EM			*EM + SS*		
	Early first	*Late first*	*Second*	*Early first*	*Late first*	*Second*
Normal	7	9	7	5	5	8
Accel.*	73	57	24	48	48	22
ED	16	34	11	13	32	11
Accel. + ED	32	44	6	26	41	7
VDa	2	11	53	5	16	43
VDb	0	2	11	0	4	15
VDc	4	0	0	0	0	1
LD	7	4	1	3	2	1
VDa + ED	6	21	26	3	21	17
VDb + ED	0	2	0	1	0	0
VDc + ED	0	0	0	0	0	0
LD + ED	4	8	3	1	8	0
LD + VDa	2	5	7	1	3	9
LD + VDb	2	6	7	0	2	5
LD + VDc	1	0	0	1	0	0
None recorded	39	21	47	40	3	27

*Accel. = accelerations; ED = early decelerations; VDa = mild variable decelerations; VDb = moderate variables; VDc = severe variables; LD = late decelerations. Early first stage of labor ≤5 cm; late first stage of labor >5 cm; second stage = complete dilation to delivery.

Table XII. Routes of delivery

	Aus (N = 232)	*EM (N = 233)*	*EM + SS (N = 230)*	*Total (N = 695)*
Vaginal deliveries	219 (94%)	192 (82%)	204 (88%)	615 (88%)
Cesarean section, non–fetal distress	12 (5%)	25 (11%)	18 (8%)	55 (8%)
Cesarean section for fetal distress	1	16 (7%)	8 (3%)	25 (4%)
	99%	100%	99%	100%

$p < 0.005$ (sig). This chi-square test was computed by combining the last two rows of this table.

no differences in the distribution of these low scores (Table XIX).

Neonatal morbidity was recorded along with various clinical judgments as to the need for more than ordinary care. The data are displayed in Table XX. There were very few serious problems and the number of infants who were affected is smaller than the number of reported events since sometimes sick infants had more than one illness. There were no significant differences among the three study groups with respect to neonatal morbidity.

Comment

Two primary conclusions emerge from this investigation on the differential effects of fetal monitoring: (1) electronic fetal monitoring with or without scalp sampling did not improve perinatal outcomes over that achieved by auscultation alone; (2) the cesarean section rate was much higher among electronically monitored patients.

While confident these conclusions are justified by our study results, we do not wish to imply that they are to be generalized to other populations in other institutional settings. For example, very premature or low-birth-weight infants (less than 2,000 grams or less than 34 weeks' gestation) were excluded from this study. The neurologic status of these infants could not be assessed by the Brazelton test. Gross prematurity is, at present, the overwhelming risk factor associated with neonatal death and morbidity. Retrospective studies have repeatedly indicated statistically significant improvements in the outcomes among less than 1,500 grams premature infants.[9, 10, 17] However, as yet no prospective controlled studies have been done in these weight and gestational age ranges.

There are many studies that strongly suggest the efficacy of electronic fetal monitoring in improving perinatal outcomes. Most of the past studies of fetal monitoring have been retrospective or, when prospective, have not included comparable control groups.[6, 8–10] In the controlled clinical trials reported to date, three have studied high-risk patients—Haverkamp[14] and Renou[7] and their co-workers and the present report—and one—Kelso and associates[24]—studied low-risk patients. The two Denver studies, which excluded grossly premature infants, showed no differ-

Table XIII. Modes of delivery

	Aus	*EM*	*EM + SS*	*Total*
Vaginal:	219 (94%)	192 (83%)	204 (88%)	615 (87%)
SSCVD*	165 (71%)	126 (54%)	149 (65%)	440 (63%)
ELF	50 (22%)	53 (23%)	46 (20%)	149 (21%)
Midforceps	0 (0%)	4 (2%)	3 (1%)	7 (1%)
Ind. forceps—FD	4 (2%)	7 (3%)	5 (2%)	16 (2%)
Breech	0 (0%)	2 (1%)	1	3
Cesarean section:	13 (6%)	41 (18%)	26 (11%)	80 (12%)
CS—non-FD	12 (5%)	25 (11%)	18 (8%)	55 (8%)
CS—FD	1	16 (7%)	8 (3%)	25 (4%)

*SSCVD = Sterile spontaneous controlled vaginal delivery; ELF = elective low forceps; Ind. forceps—FD = forceps delivery indicated for fetal distress; CS—non-FD = cesarean section for reasons *other than* fetal distress.

Table XIV. Anesthesia at delivery

	Aus (*N = 232*)	*EM* (*N = 233*)	*EM + SS* (*N = 230*)	*Total* (*N = 695*)
No anesthesia	31 (13%)	20 (9%)	19 (8%)	70 (10%)
Local, pudendal	140 (60%)	118 (51%)	147 (64%)	405 (58%)
Epidural, SAB*	48 (21%)	53 (23%)	40 (17%)	141 (20%)
General	11 (5%)	38 (16%)	22 (10%)	71 (10%)
Not recorded	2 (1%)	4 (2%)	2 (1%)	8 (1%)
	100%	101%	100%	99%

*SAB = Subarachnoid block (saddle or spinal). Note: Difference in frequency of general anesthesia reflects increased number of cesarean section deliveries performed in the two monitored groups.

Table XVA. Postpartum infections among mothers having vaginal deliveries

	Aus (*N = 219*)	*EM* (*N = 192*)	*EM + SS* (*N = 203*)
No antibiotics, no infection	195 (89%)	164 (86%)	186 (92%)
Prophylactic antibiotics, no infection	17 (7.5%)	18 (9%)	10 (5%)
Prophylactic antibiotics, infection	1 (0.5%)	2 (1%)	2 (2%)
Treated documented infection	6 (3%)	8 (4%)	5 (2%)

ences in perinatal outcomes. Renou's controlled study did show differences in perinatal outcomes, especially improved neurologic status in the electronically monitored infants, but the range of gestational ages is unclear. The controlled trial by Kelso and associates[24] of low-risk obstetric patients showed no difference in perinatal outcome in 504 patients between auscultation and monitoring.

We are impressed that good prenatal care combined with good clinical intrapartum obstetric care, regardless of exact fetal monitoring techniques, results in excellent perinatal outcomes. Although we studied the patients with the highest risk status in a hospital with a high-risk population, the fact that the grossly premature infants were excluded reduces the morbidity and mortality rates to very low levels. Indeed, Neutra and associates[25] noted in their recent paper, remarking on neonatal death of term-size infants: "one of the striking findings of this study is that the majority of babies have a risk of neonatal death at or below one per thousand."

Table XVB. Postpartum infections among mothers having cesarean sections

	Aus (*N = 13*)	*EM* (*N = 41*)	*EM + SS* (*N = 26*)
No antibiotics, no infection	0 (0%)	1 (2%)	3 (12%)
Prophylactic antibiotics, no infection	12 (92%)	35 (85%)	18 (69%)
Prophylactic antibiotics, infection	1 (8%)	5 (12%)	4 (15%)
Treated documented infection	0 (0%)	0 (0%)	1 (4%)

Combining the two controlled trials in Denver totals almost one thousand patients who were followed clinically in labor by either electronic monitoring (475) or auscultation (473). Perinatal outcomes were the same in all measured categories and included no intrapartum deaths. There were five neonatal deaths, one in the auscultated and four in the electronically monitored groups. To attempt to show a beneficial effect of moni-

Table XVI. Mean Apgar scores + SEM*

	Aus (N = 232)	*EM (N = 233)*	*EM + SS (N = 230)*
Apgar score—1 minute	7.53 ± 0.1	7.35 ± 0.12	7.44 ± 0.1
Apgar score—5 minutes	8.82 ± 0.06	8.80 ± 0.08	8.67 ± 0.05

*Standard error of the mean.

Table XVII. Distribution of Apgar scores

	Aus N = 232	*EM N = 233*	*EM + SS N = 230*	*Total N = 695*
At 1 minute:*				
0-3	11 (5%)	14 (6%)	10 (4%)	35 (5%)
4-7	61 (26%)	63 (27%)	63 (27%)	187 (27%)
8-10	160 (69%)	156 (67%)	157 (68%)	473 (68%)
	100%	100%	99%	100%
At 5 minutes†:				
0-3	1	4 (2%)	0	5 (1%)
4-7	13 (6%)	8 (3%)	12 (5%)	33 (5%)
8-10	218 (94%)	221 (95%)	218 (95%)	657 (94%)
	100%	100%	100%	100%

*p = 0.94 (NS).
†p = 0.17 (NS).

toring under the conditions of these two studies would epidemiologically require an enormous number of term high-risk patients, as the adverse events or end points being used seem to be very infrequent. Furthermore, since no differences in outcome were found in these studies among high-risk patients, it would seem very unlikely that a low-risk term patient experiencing a normal labor would benefit from monitoring if she is properly auscultated.

The method of delivery was affected by the manner of intrapartum monitoring. There were distinct differences in the rates of cesarean section, especially between the Aus (6%) and the EM groups (18%). This followed an increased diagnosis of both fetal distress and failure to progress (e.g., cephalopelvic disproportion) in the EM patients. Thus, it appears that the EM laboring patient is at greater risk for cesarean section. The option of scalp sampling with electronic monitoring also had a significantly higher cesarean section rate for fetal distress, when compared to auscultation (3% vs. 0.4%). There was a similar trend for other indications (8% vs. 5%) but this did not achieve statistical significance. Note that in all categories, the cesarean section rate for those monitored with scalp sampling was lower than for those with electronic monitoring alone. This apparent difference did not achieve statistical significance. However, other investigators have previously noted the high rate of false-positive diagnosis of fetal distress with ominous patterns. Only 20 to 40% of ominous patterns will be associated with fetal pH values that are considered acidotic. It is for this reason that Beard,[18] James,[19] Quilligan,[20] and others have argued for scalp sampling as an integral part of any program of electronic fetal monitoring. If one relies on the fetal monitor, fetal scalp sampling may be required in order to more carefully distinguish stress from distress.

Paradoxically, the perception of the need to intervene during labor and to deliver the fetus by cesarean section was reduced by having less information about the auscultated patients. The difference in the rate of cesarean section for both fetal distress and failure to progress (CPD) is statistically significant between the EM and the Aus patients. We are left with the impression that nurses auscultate with a different perspective since the advent of the electronic monitor, which has provided much more information about fetal heart rate patterns. This may explain the divergence of our findings from those of the study published by Benson and associates[21] in 1968, which noted a poor correlation between auscultation and fetal outcome.

A perplexing observation was the significant increase in cesarean sections performed for reasons other than fetal distress among electronically monitored patients as compared to auscultated ones. Most of these were done because of CPD or failure to progress in labor. Why this is so is unclear. However, in the two other controlled trials of electronic monitoring, investigations showed somewhat similar findings. Kelso and associates[24] found a significantly increased rate of cesarean section in the electronically monitored versus auscultated patients for reasons other than fetal distress in their low-risk patients. Renou and associates[7] noted that cesarean sections for reasons of CPD or failure to progress were more common among patients being followed by monitoring and scalp sampling than among auscultated patients, but the difference was not significant.

There have been concerns about maternal postpartum infections, infant infections, and sepsis related to direct fetal heart rate monitoring. Among the three groups of women delivered vaginally, there were no differences in the rate of postpartum infections, all being approximately 3%. Having an internal monitor prior to vaginal delivery did not increase postpartum infections. The infants showed no differences among the three groups in the rate of neonatal sepsis with the actual number, two (both viral), so low that sepsis in relatively term-size internally monitored patients does not appear to be a significant problem.

Because of the high rates of postpartum infection in laboring patients undergoing cesarean sections at Denver General Hospital, most of the patients were given prophylactic antibiotics. There were no differences be-

Table XVIII. Umbilical cord blood gases (mean − SEM)

	Aus (N = 211)	*EM (N = 215)*	*EM + SS (N = 212)*	*p values*
Arterial:				
pH	7.27 ± 0.005	7.26 ± 0.005	7.27 ± 0.005	0.16 (NS)
Po_2	15.8 ± 0.36	16.0 ± 0.39	16.1 ± 0.38	0.8 (NS)
Pco_2	38.9 ± 0.63	40.5 ± 0.65	39.4 ± 0.60	0.17 (NS)
Venous:	*(N = 228)*	*(N = 230)*	*(N = 225)*	
pH	7.36 ± 0.005	7.35 ± 0.005	7.36 ± 0.004	0.65 (NS)
Po_2	27.4 ± 0.43	27.9 ± 0.41	28.0 ± 0.43	0.54 (NS)
Pco_2	29.5 ± 0.45	31.0 ± 0.41	29.8 ± 0.39	0.03 (sig)

Table XIX. Distribution of umbilical cord blood pH's

	Aus (N = 211)	*EM (N = 215)*	*EM + SS (N = 212)*	*Total (N = 638)*
Arterial:*				
≤7.20	34 (16%)	39 (18%)	38 (18%)	111 (17%)
>7.20	177 (84%)	176 (82%)	174 (82%)	527 (83%)
	100%	100%	100%	100%
Venous†:	*N = 228*	*N = 230*	*N = 225*	*N = 683*
≤7.25	13 (6%)	14 (6%)	17 (7%)	44 (6%)
>7.25	215 (94%)	216 (94%)	208 (93%)	639 (94%)
	100%	100%	100%	100%

*p = 0.83 (NS).
†p = 0.7 (NS).

Table XX. Neonatal morbidity

	Aus	*EM*	*EM + SS*	*Total*
Conditions:				
Respiratory distress	9	12	18	39
Pneumonia	0	2	2	4
Seizures	2	2	0	4
Sepsis	0	0	2	2
Meningitis	0	0	0	0
Total	11	16	22	49
Additional care:				
Intensive nursery care	29	23	29	81
Required antibiotics	15	15	20	50

tween the postpartum infection rates with or without internal monitoring when prophylactic antibiotics were used.

A nurse was assigned to each mother in the study, whether electronically monitored or auscultated, in order to assure the quality and uniformity of patient care as well as the accuracy of data collection. This type of one-to-one nurse-to-patient ratio may be impractical and is impossible in many clinical situations. The effectiveness of less rigidly auscultating and recording FHT's is an unknown. However, the laboring patient needs more nursing care than can be provided by an electronic monitor. It must be realized that considerable time is spent by nurses in setting up machines, checking on monitors' functioning, and in their own inservice training for this task. The feeling that monitoring reduces the cost of nursing care has not been carefully studied from total cost, time, benefit, or training perspectives.

Fetal monitors are now receiving almost universal use in obstetric practice. When 68 hospitals were surveyed by the Senate Subcommittee on Health, which is studying obstetric practice, it was found that all the hospitals used monitors. Sixty-four percent used monitors on almost all labors.[22] This use creates a number of problems with respect to interactions between patient, physician, and institutions. For example, what does the doctor or hospital do if a patient refuses monitoring? What does the patient do if the doctor or hospital insists upon monitoring?

Clearly, more controlled, well-designed perinatal studies (including long-term follow-up) are needed to evaluate the proper clinical role of electronic fetal monitoring. It has never been more important to separate the needed technology from the extraneous technology. More information and more sophisticated techniques do not necessarily improve outcomes. The support of both the public and the medical community is needed for more randomized prospective controlled studies to provide evidence which will allow both the physician and the patient to make informed, reasoned decisions on the effectiveness of various medical interventions.

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Discussion

DR. PRESTON V. DILTS, JR., Memphis, Tennessee. In their continued, difficult study, the authors have concluded: (1) electronic fetal monitoring and monitoring plus scalp pH sampling do not improve fetal outcome as compared to standard auscultation; (2) the cesarean section rate is several times higher in patients with electronic monitoring but not in patients with scalp sampling.

These conclusions are specifically limited to patients (1) at term, (2) with high-risk pregnancy, and (3) in a city-county hospital.

There are several problems. In their previous paper, Haverkamp and associates[1] found a difference in the incidence of abnormal heart rate tracings between the auscultated and monitored groups. Dr. Morton Stenchever discussed this, suggesting that the groups were not similar. There also was a higher cesarean section rate in the monitored group for reasons other than distress. No attempt is made to answer these questions now nor were they mentioned in the review of literature.

The authors ruptured membranes as early as possible in the monitored patients. This may increase the incidence of heart rate abnormalities and may influence the course of labor. Scalp pH definitely is lower with early rupture of the membranes.

The reasons for which patients were classed as high risk are not given. The number and degree of severity of the patients with diabetes, hypertension, and other illnesses must be presented and discussed.

Scalp sampling was done on 44 of the patients. No data or discussion are presented. In the tables presenting nonreassuring and ominous heart rate tracings, abnormalities increase as labor advances. The scalp sampling group had the highest rate of abnormality, with the monitored group second. However, the cesarean section rate is lower in the scalp sampling group. Is this because of scalp pH or some other reason?

The types of heart rate abnormality are presented in a very involved table. An outside observer agreed 90% of the time. A 10% change in the numbers in any group might distinctly bias the outcome.

There was a 5% cesarean section rate for CPD or failure to progress in the auscultated group without fetal distress. This rose to 11% in the monitored group and 8% with scalp sampling. The difference is difficult to explain. The increased incidence of fetal distress in the monitored group as opposed to the scalp sampling and auscultation groups is apparently because the monitor picks up variations in heart rate which may appear ominous and because scalp sampling reassures, avoiding cesarean section. However, data are not presented to support this position.

Finally, in the discussion, the authors add the numbers in this report with those in their previous paper. This is adding apples and oranges to pears and comparing them to grapefruit. I am sure the authors are aware of the vast differences in the two studies.

My conclusions, based on the data in the manuscript, are: (1) Scalp sampling reduces the incidence of cesarean section to that found with auscultation. It is implied that the level of confidence in that decision is greater with monitoring plus scalp sampling than with auscul-

tation alone. (2) There are no differences in immediate outcome between the scalp sampled and the auscultated groups or the monitored group. However, long-term results are needed and the paper is not complete until they are available. (3) There are many unanswered questions. Why is the cesarean section rate higher with monitoring and somewhat lower with scalp sampling for reasons other than fetal distress? Our impression is that CPD is diagnosed more often with monitoring because monitoring indicates that labor is "adequate." In the "old days" we waited at least 4 hours before deciding there was failure to progress. Second, does early rupture of the membranes lead to fetal distress and/or cephalopelvic disproportion? Caldeyro-Barcia and others[2] felt that membranes should not be ruptured unless there is need for a scalp electrode. If this is the case, why the improvement with scalp sampling? Finally, the conclusions apply only to high-risk patients at term in a city-county hospital.

The authors are again to be congratulated. They have begun the long process of trying to figure out what the value of monitoring is. However, their study has deficiences which must be answered.

Hellegers[3] has proposed that a study of cesarean section may be the correct approach. After all, cesarean section is the ultimate treatment of the abnormalities discovered by monitoring. He suggested alternate vaginal and abdominal delivery for high-risk patients with or without a trial of monitoring. The issue of prematurity also needs to be approached. Finally, given the level of nursing expertise and staffing patterns in most OB units, how does this transpose to the real world? Is not monitoring better and less expensive than sporadic auscultation?

I hope both the proponents and opponents will refrain from debating or presenting publicly until a scientifically sound study of enough patients can be conducted to provide valid conclusions. As an example, it was reported in the January 1, 1978, issue of *OB GYN News* that Dr. Haverkamp had presented some of these data before the American Public Health Association some time in 1977.

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DR. ROBERT A. MUNSICK, Indianapolis, Indiana. In 1959 Walker[1] reported a prospective study from South Africa on operative versus conservative management of fetal distress. Among his most notable findings was the fact that operative intervention for fetal distress did not improve the perinatal mortality rate unless other obstetric complications such as disproportion were extant. In his editorial discussion of this study, Eastman[2] stated, ". . . the author reviews the widely divergent opinions of various authorities on the significance of the supposed signs of fetal distress; and, on the basis of this and other evidence, it is clear that we need much more information on this important question than we now possess. It seems probable that prolonged electronic monitoring of fetal heart rates, when correlated with meconium stained fluid, fetal outlook and other circumstances, may provide some portion at least of the detailed, precise information we should like to have. Several such studies are now under way and let us hope that they serve this end."

Just as it is a sad commentary on our specialty that it has taken nearly a score of years to produce four objective prospective studies to answer Eastman's suggestion, we can be proud of the fact that these studies have been done, that those from the Denver General Hospital have both been presented to this Association, and that each by Haverkamp and associates has been masterfully designed and is among the best clinical investigations performed in obstetrics.

From the data so far reported, it appears clear that EM does not improve fetal or neonatal survival or immediate performance. Long-range data are still wanting. In this study reported to us today by Dr. McFee, the group has objectively answered the critics of the first study. I have some questions to ask, mostly for clarification:

(1) In the first study, ultimate management decisions were made by three staff members with very similar approaches to obstetrics. Was this the case in the current study? (2) Previously, febrile morbidity was reported, not infections. Do these equate and what were the particular infections? (3) What were the types of abnormal labor in each of the three groups? (4) What were the indications for oxytocin in each of the three groups? (5) Among labors induced or stimulated with oxytocin, was EM of significant advantage to the fetuses? (6) What were the total hospital days and costs for the mothers and babies of each group? (7) Were gravidas with prior cesarean sections admitted to any groups and, if so, did their presence influence the rate of cesarean section? (8) What, exactly, were the indications other than fetal distress for the cesarean sections in each group? (9) From the last question, do the authors have a hypothesis to explain the high cesarean section rate with EM? (10) Will the authors now or in their subsequent papers better define "high-risk" status? The system of Goodwin, Dunne, and Thomas, to which they refer, does not include parturition and has a 0 for least, 10 for greatest risk score. In the current study, many patients were quite properly included

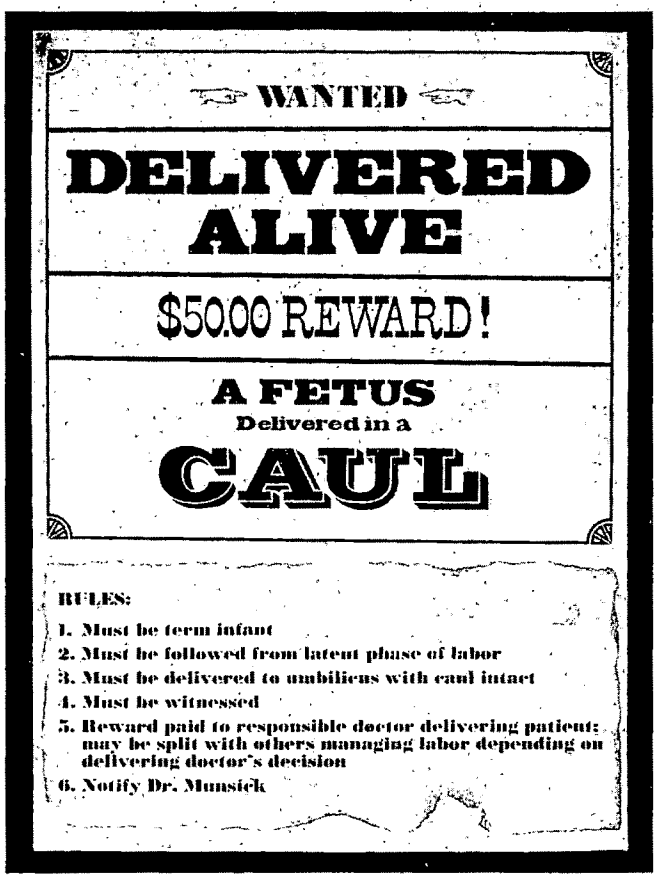


Fig. 1. "Wanted" notice posted in residents' lounge.

because of labor abnormalities, but these should be defined, and the scoring system goes 10 for least, 0 for greatest risk. (11) Finally, will Dr. McFee not attempt to make a recommendation concerning the use of EM? What system of monitoring is now being used at Denver General Hospital?

Unless EM is shown incontrovertibly to benefit the neonate, my experience with it leads me to recommend against its frequent use. It has had pervasive negative effects on obstetric practice and training. What effects are these?

External monitoring restrains patients in bed in early labor. It encourages assumption of the supine position. Competent abdominal examination is made impossible and few are those who will even temporarily remove the straps once they are applied. Nurses and physicians regularly misinterpret external tocographs as showing uterine tonus and contractile amplitude. They tend not to or cannot palpate uterine contractions with straps in place.

With internal EM, pelvic examinations are less than competently done for fear of dislodging electrodes or catheters. Adequate assessments of fetal position, presentation, and pelvic architecture are less often sought.

Early amniotomy becomes a routine reflex; how else can the scalp electrode be placed? For many patients, this practice then requires oxytocin for augmentation or even for induction of labor. Attempts by me through entreaty, counseling, and even cajolery failed to influence this practice. What finally worked for a while is shown in Fig. 1. Incredible as it may seem, four infants were delivered in caul within 10 days of posting this notice!

Perhaps worst of all, EM has dehumanized obstetrics. We cannot divert our eyes or ears from EM's alluring LED's, beeps, and stylus-chattering graphs. We no longer listen to, talk with, gaze upon, or touch our patient. We will deny her analgesia to protect the graph from a loss of variability.

Is there evidence of this growing dehumanization, evidence other than the public push for home deliveries? I would like you to entertain a hypothesis which will explain on the basis of dehumanization with EM the increased rates of both fetal distress and cesarean section. We begin by restraining a woman early in her labor. We allow her to see the EM's chattering stylus and its winks; often we even torture her unnecessarily with hours of its staccato sounds at 150 beeps per minute and we watch the monitor and not her. She dare not interrupt our silent vigil. Anxiety gives way

to fright and anger. Something—possibly catecholamines—causes her to have abnormal contractions and these in turn cause arrest of labor and sometimes diminished uteroplacental blood flow. The supine position aggravates the latter. And we then apply the modern-day obstetric panacea—cesarean section. If you doubt that internal fetal monitoring can influence labor, see Fig. 1 of the paper by Sokol, Zador, and Rosen.[3]

This explanation may be incorrect, but there can be no doubt that the cesarean section rate doubles in association with, if not because of, EM. If Neutra and associates (Ref. 25 of the paper under discussion) are correct in estimating that EM may save 1 in 1,500 or more infants, let's extrapolate these data in terms of what is seldom mentioned in this enormously important controversy—*maternal death.* The cesarean section mortality rate is at least 1 in 1,000 operations.[4] In 1975, there were 3,150,000 live U. S. births. If EM saves 1 in 1,500, it would have saved 2,000 babies in 1975 if applied to all laboring patients. Assuming an 8% over-all cesarean rate without EM, 240,000 cesarean deliveries would have occurred in 1975 with 240 maternal deaths. Doubling the cesarean rate with EM would then kill 480 women. For 2,000 babies saved we sacrificed 240 women—one woman for eight babies. Should not this information be provided to gravidas before obtaining their informed consent for EM? Indeed, should not informed consent be obtained before instituting EM?

This issue is so important that our Association and the A.C.O.G. through the N.I.H. should begin at once a massive, prospective, collaborative study to settle the question: For whom is EM beneficial? Only through such a large study can the question of whether or not to monitor premature fetuses be answered.

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Dr. Stephen L. Bloom, Waterloo, Iowa. How soon after observing abnormalities with monitoring was action instituted to evaluate the abnormality?

In reviews of monitoring at some institutions there can be a lag time, depending on how busy the staff is between the time an abnormality is picked up and the time it is evaluated. If there is a lag time, then I think that knocks down the ultimate result and quality to the level of the unmonitored patients.

The next comment that I have is in relation to the last discussant. I do not feel that electronic fetal monitoring is a cause of physician insensitivity in dealing with patients, nor is electronic fetal monitoring a cause of inept pelvic examinations. I do not see any cause-and-effect relationship. I do not think monitoring has anything to do with treating patients impersonally and improperly.

Dr. Frank H. Boehm, Nashville, Tennessee. While we are going through the years of arguments and discussions on fetal monitoring, I hope that we do not lose sight of the fact that the monitor is an instrument that gives us information pertaining, in part, to fetal well being. Those who would not support its use, in my opinion, are arguing against quality information with a very low risk-benefit ratio.

We put a lot of emphasis on fetal heart rate, yet few individuals address themselves to the very important information that comes from the uterine activity line: the ability to make a more accurate diagnosis of CPD or to monitor patients who are being given oxytocin infusion to stimulate labor or drugs to stop labor are important parameters of fetal monitoring and clearly an aid to optimal care.

In most institutions where routine fetal monitoring has been instituted, the fetal death rate in labor has been reduced to close to zero. This is certainly a significant improvement from the two to four per thousand fetal deaths in labor that have occurred in other studies without fetal monitoring.

The Cesarean section rate, in my opinion, goes up because we have not educated our medical personnel on the proper interpretation of the data. Our cesarean section rate at Vanderbilt has been the same in the last 4 years despite the fact that we have monitored all of our patients on a continuous basis.

Patients who are monitored in our institution are given quality, considerate, and kind care by our nurses. The monitor does not nor should it ever replace that kind of care.

Despite this paper's results, I still believe that fetal monitoring is an extremely important device to reduce maternal and fetal death and morbidity.

Dr. Warren M. Crosby, Oklahoma City, Oklahoma. While this paper suggests that fetal monitoring does bad things and the absence of the fetal monitor does good things, I submit that Drs. McFee and Haverkamp really believe in fetal monitoring. Else why would they hire a nurse and plug her in to the patient to listen to the fetal heart rate every 5 minutes? You cannot do that on the usual hospital labor ward without hiring a special nurse and having a special setup for each individual patient; that can be accomplished only in a study like this. So the fetal monitor in this case is human rather than electronic.

Anyone who looks at hours of fetal monitor strips will see many horrible-looking fetal cardiac deceleration patterns, acceleration patterns, and occasionally lack of beat-to-beat variability. In many of these the

baby is well, but in a few the baby is sick. My point here is that the fetal monitor does not tell you when the fetus should be delivered abdominally, it merely is a screening device that tells the physician when the fetal cardiac response to labor is no longer proceeding normally. When this occurs, the physician should re-evaluate the situation to find out whether a maternal problem has developed. Then he must evaluate the degree of fetal compromise by scalp blood gas analysis if the alarming fetal distress pattern continues on the monitor. With fetal scalp blood pH it is possible to select the acidotic fetus from the one with an overreactive cardiovascular system. This then enables the obstetrician to perform cesarean section only on those fetuses that are in jeopardy of dying before labor could be expected to terminate naturally or by forceps delivery. This paper does not negate the usefulness of fetal monitoring, as the authors suggest. Their results indicate that if you monitor the fetus carefully enough—by nurse or by machine—and evaluate those fetuses in potential jeopardy, intrapartum death can be essentially eliminated. The key phrase here is "monitor the fetus carefully enough." In most hospitals that can be accomplished only by an electronic fetal monitor.

DR. G. ERIC KNOX, Minneapolis, Minnesota. I have a question regarding statistical analysis. Assuming that the issues raised by Dr. Dilts regarding the comparability in general, and of obstetric risk in particular, between the groups is satisfactorily addressed, this study may still not answer the question it was designed to. As Dr. Munsick pointed out, and as was pointed out in the recent publication from Boston, approximately 1,100 term babies need to be monitored to demonstrate an effect on the mortality rate. Therefore, even though the current study is impressive with regard to the number of patients that have already been enrolled, I am wondering from a statistical point of view whether the numbers needed to actually demonstrate an effect or lack of effect of monitoring on mortality can ever be achieved in any study, simply because they are so high.

DR. MCFEE (Closing). Why there was a higher cesarean section rate for reasons not due to fetal distress in the monitored groups over that auscultated I do not know. At least two other studies on fetal monitoring from other parts of the world have shown essentially the same thing. I think Dr. Munsick's hypothesis may very well play a role here. I am convinced that the presence of a monitor and the events which ensue do indeed frighten a considerable number of women, especially among the indigent and the uneducated. This may, in turn, contribute to uterine inertia and failure to progress normally in labor.

Dr. Dilts noted that we have left out many specific diagnoses in our list of reasons why patients were deemed high risk. We did not tabulate these as they include a multitude of conditions, most of which are so small in number that they probably would not make any difference anyhow. One thing to remember in doing a randomized study of this sort is that it is impossible to make the three groups totally equal in all respects and still remain randomized. We have shown things this morning which indicate that the three groups on retrospect were equal in many respects.

I agree that combining the results of our two studies is probably not a good comparison. However, when one get down to the basics, there was a considerable difference in the number of cesarean sections between monitored and auscultated patients.

As for Dr. Bloom's question about how soon after abnormal patterns was something done, I would say this was immediately because the nurses were with the patient on a one-to-one basis.

I agree with all the comments of Dr. Boehm regarding the many things about which the monitor can inform the physician.

With respect to Dr. Crosby's comments, I would like to correct one misinterpretation: Perinatal outcomes of auscultated mothers were not better than those of monitored patients; they were equal. I think this is important. I agree with him that it is virtually impossible in most institutions to obtain this kind of nursing care on a one-to-one basis throughout all labors. This brings up the necessity of investigating costs when we are considering both the use of fetal monitoring and the use of nurses for intrapartum surveillance.

Another important question is how many patients we really need to show a difference between monitoring, monitoring with scalp sampling, and auscultation. This is particularly relevant among low-risk patients.

To answer Dr. Munsick's question on my feelings about the use of monitoring, I believe electronic monitoring is an easy, useful tool for the observation of labor. This is especially true in conjunction with scalp sampling and also in our high-risk units, which have a heavy volume of patients and often a relative lack of physicians and nurses to care for them. However, the feeling currently being expressed in many quarters that *all* labors must be monitored or, to put it medicolegally, that it is malpractice *not* to monitor given labor, is simply not justified. That auscultation can do as good a job has important implications for the small rural hospital which may not have the monies to buy and maintain monitoring equipment or be able to give correct interpretation to the tracings. This may also have some importance for some of our larger hospitals which deal primarily with a low-risk, term pregnant population. In short, universal electronic fetal monitoring is currently being advocated before its usefulness in all labors for both the mother and fetus and cost-benefit relationships have been adequately assessed.

Lastly, I would like to re-emphasize one of Dr. Munsick's comments that in recent years we have perhaps overemphasized the well being of the fetus and have largely pushed the mother into the back of our minds. I think this needs to be corrected.

Perinatal deaths in twin pregnancy

A five-year analysis of statewide statistics in Missouri

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Analysis of computer-stored State of Missouri birth and death records over a 5 year period revealed 3,594 twin pregnancies (1.02% of all pregnancies), which accounted for 10.1% of the perinatal deaths. The mean birth weight according to weeks of gestation was computed for the pregnancies with no complications noted prior to labor and the perinatal mortality rate was determined. Complications of pregnancy were evaluated. Low birth weight appears to be the major factor in the elevated perinatal death rate in twin pregnancy, with a significant elevation of the perinatal death rate noted with labor prior to 36 weeks, any episode of hemorrhage, or premature rupture of membranes. A more liberal use of cesarean section currently shows no effect in altering the perinatal mortality rate. Programs are suggested to increase early detection and appropriate consultation and referral of multiple pregnancies in a statewide comprehensive effort to decrease the perinatal mortality rate in twin pregnancy. (AM. J. OBSTET. GYNECOL. 134:413, 1979.)

LEGISLATION established in Missouri in 1974, a high-risk maternal and child care program under House Bill No. 1686. The program's intent was to ensure that pregnant women and infants at high risk for developing mental retardation would not be denied needed health care because of inadequate funds. Thus, the program was conceived as an attempt to prevent mental retardation. As part of this over-all plan, computerization of birth certificate data in Missouri and analysis of various conditions contributing to increased perinatal and neonatal risk were performed by the Missouri Division of Health to gain a better statistical understanding of the problem of health care delivery in Missouri.

Most computer research previously done has been on singleton pregnancies. Because of the difficulty of data management in multiple pregnancies, it was felt that this initial statistical analysis would aid in establishing computer analysis of other high-risk pregnancies. In addition, multiple pregnancy is one of the major areas of perinatal death within this state.

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Method

Data for this study were acquired from the official vital statistics of Missouri. It is believed that over 99% of all births are recorded at the time of occurrence and more than 98% of recorded births in Missouri occur in hospitals. An extensive program of editing and querying data of birth and of fetal and infant death certificates has been in existence since 1974. In 1974 work was begun on matching birth with infant death certificates and now an ongoing file exists, starting with the 1972 calendar year.

In conjunction with this an ongoing file of births and fetal deaths exists, starting with the 1972 calendar year. The present study uses both the matched birth–infant death file and the birth–fetal death file to create a cohort file on twins. To select out and match twins, the following method was used. If the number born equalled two, the following items were matched by computer: last name of child and parents, date of birth,

Table I. No complication noted before labor, complications intra- or postpartum, and live birth weight

Weeks' gestation	Total pregnant	% pregnant	Cesarean section	Mean wt. (gm)	S.D.	% Under 1,501	% 1,501-2,500	Still births /1,000	Neonatal deaths /1,000*	Perinatal deaths /1,000
27L	105	2.9	2.8	800	451	9[illegible].7	4.7	200	638	838
28-31	145	4.0	4.1	1,355	401	6[illegible].6	30.0	82	400	482
32-33	171	4.7	5.8	1,843	425	1[illegible].5	76.6	32	87	119
34-35	354	9.8	6.7	2,101	442	[illegible].1	75.1	15	48	63
36-37	550	15.3	7.8	2,428	420	[illegible].2	55.2	17	18	35
38-39	712	19.8	9.1	2,646	471	[illegible].7	36.0	16	4	20
40-41	527	14.6	10.0	2,757	491	[illegible].6	29.2	22	12	35
42-43	185	15.1	10.8	2,740	501	[illegible].8	30.8	13	2	16
44P	82	2.2	8.5	2,663	508	5.7	31.7	42	0	42
Total no. complications	2,831	78.7	8.1	2,394	648	11.4	43.9	29	62	91

*Neonatal death rate figured from 100% of pregnancies, which includes fetal deaths.

and state and county of recording. For those records where the number born was unknown, or the column for the date of the previous live born or previous fetal death is blank or not of the same date of delivery, the born number is assigned as one. A manual check was performed to make sure that there was no evidence of their being twins.

The birth order was assigned on the basis of considering the twin with the lowest birth–fetal death certificate number as first born. Where a certificate noted that another twin was a fetal death but no certificate existed, matching certificates were made for the fetal deaths. Where a certificate noted that the other twin was a live birth but no certificate existed, dummy live birth certificates were made. The data for the dummy certificates were acquired by using variables obtained from the existing certificate.

The computer-stored data were then analyzed from January, 1972, through December, 1976, with regard to no complications noted before labor, weeks of gestation, total pregnancies, percent of pregnancies, percent of cesarean sections, percent of abnormal presentations (at least one twin breech or transverse), the mean birth weight and the percentage under 1,500 grams, between 1,500 and 2,500 grams, and greater than 2,500 grams, stillbirths, neonatal deaths, and the combined perinatal mortality rate were all evaluated. The data were then further analyzed with regard to complications noted before labor in a hierarchical form. These included abruptio placentae, placenta previa, other episodes of hemorrhage, diabetes mellitus, premature rupture of membranes, toxemia, major medical complications of pregnancy, miscellaneous complications of pregnancy, Rh incompatibility, obesity, abnormal pelvis–cephalopelvic disproportion–fetal distress (ACF), previous cesarean section, total complications category, total without complications prior to labor, and a page total. Risk ratio was calculated according to a formula of the percent of all perinatal deaths divided by the percent of all pregnancies.

Tests for the significance of difference between two rates were performed for comparison of the significant values utilized during the analysis of data. In an effort to evaluate the use of a hierarchical form of ranking complications, nonhierarchical analysis of complications noted before birth was performed and in all cases statistical analysis was not altered. There were also certain complications noted before labor in the groups of major medical and miscellaneous complications of pregnancy which, while having significant N values, contained such a wide diversity of factors that analysis was not performed in these categories; however, they were added into the total complications.

Results

Demographic data. During the 5 year period there were 3,594 pairs of twins born, a total incidence of 1.05% of the pregnancies in the state. These pregnancies accounted for 7.06% of all stillbirths, 13.03% of neonatal deaths, and 10.10% of all perinatal deaths during this period of time.

The mean birth weight was 2,349 grams, with a standard deviation of 677 grams, and 57.7% were less than 2,500 grams. Complications noted before labor were present in 21.2% of all twin pregnancies with premature rupture of membranes accounting for 5.0% and toxemia of pregnancy 4.9%, followed by previous cesarean section 2.1%, ACF 2.0%, and abruptio placentae 1.5%. The over-all stillborn rate was 40 per thousand, with a neonatal death rate of 76 per thousand and a perinatal death rate of 116 per thousand (Table I).

Birth weight, gestational age, with complications noted prior to labor. The analysis was performed in a hierarchical manner; abruptio placentae, placenta previa, other episodes of hemorrhage, diabetes, premature rupture of membranes, toxemia, Rh incom-

Table II. Significance of the difference between complications, no complications, and perinatal, neonatal, and fetal death rates

	Perinatal deaths			*Neonatal deaths*			*Fetal deaths*		
	No.	*Rate/ 1,000*	*Significance level*	*No.*	*Rate/ 1,000**	*Significance level*	*No.*	*Rate/ 1,000*	*Significance level*
No complications	515	91.0		351	62.0		164	29.0	
Abruptio placentae	49	490.0	0.001	28	280.0	0.001	21	210.0	0.001
Placenta previa	12	214.3	0.001	11	196.4	0.001	1	17.9	
Other hemorrhage	11	289.5	0.001	7	184.2	0.001	4	105.3	0.001
Diabetes	4	285.7		2	142.9		2	142.9	
PROM	114	316.7	0.001	80	222.2	0.001	34	94.4	0.001
Toxemia	21	58.7	0.05	9	25.1	NS	12	33.5	NS
Rh incompatible	5	131.6		3	78.9		2	52.6	
ACF	9	60.8	NS	4	27.0		5	33.8	
Previous cesarean	4	26.3		3	19.7		1	6.6	
Complications—total	320	209.7	0.001	198	129.8	0.001	122	79.9	0.001

*Neonatal death rate figured from 100% of pregnancies, which includes fetal deaths.

Table III. Significance of the difference between complications, no complications, and weight levels

	≤1.5 kg			*1.5 = ≤2.5 kg*			*>2.5 kg*		
	No.	*%*	*Significance level*	*No.*	*%*	*Significance level*	*No.*	*%*	*Significance level*
No complications	627	11.4		2,414	43.9		2,457	44.7	
Abruptio placentae	40	50.0	0.001	30	38.0	NS	9	12.0	.05
Placenta previa	20	35.7	0.001	21	37.5	NS	14	26.8	NS
Other hemorrhage	17	50.0	0.001	12	34.2	NS	5	15.8	NS
Diabetes	3	21.4		5	42.8		4	35.8	NS
PROM	123	37.7	0.001	150	46.1	NS	53	16.2	0.001
Toxemia	28	8.1	NS	163	47.2	NS	155	44.7	NS
Rh incompatible	4	10.5		21	57.8	NS	11	31.7	NS
Obesity	0	0.0		7	70.0	NS	3	30.0	
ACF	9	6.0	NS	45	31.7	NS	89	62.3	0.001
Previous cesarean	7	4.6	NS	66	43.4	NS	78	52.0	NS
Complications—total	349	24.9	0.001	590	42.0	NS	465	33.1	0.001

patibility, obesity, ACF, previous cesarean section, and complication total were recorded in Table II. These perinatal death rates were compared with the total values for the noncomplicated patient and statistically significant P levels of <0.001 were found for abruptio placentae, placenta previa, other hemorrhage, premature rupture of membranes, and total complications. Toxemia and ACF were not significant for perinatal death and the N was insufficient to evaluate on the other entities.

Neonatal death rate showed a significant level of $P < 0.001$ for three forms of hemorrhage, premature rupture of membranes, and total complications, with an insignificant level for toxemia; the remainder of the values were insufficient to evaluate.

Fetal death rate showed a significant level of $P < 0.001$ for abruptio placentae, other hemorrhage, premature rupture of membranes, and total complications. Toxemia was insignificant; the remainder of the values were insufficient to evaluate.

When the perinatal death rate was compared to birth weight with regard to complications or no complications (Table III), there was a statistically significant incidence of low-birth-weight infants (less than 1,500 grams) in association with abruptio placentae, placenta previa, other hemorrhage, premature rupture of membranes, and total complications (P level <0.001). There was no statistically significant incidence of low-birth-weight infants (<1,500 grams) in association with toxemia, ACF, and previous cesarean section. The majority of infants in the category of ACF demonstrated a statistically significant birth weight greater than 2,500 grams.

The highest number of perinatal mortality complications occurred in the miscellaneous complications of pregnancy and there was a significantly lower mean birth weight of 1,423 grams, with 72.2% under 1,500 grams and 18.8% between 1,500 and 2,500 grams, which is a statistically significant $P < 0.001$ for comparison with noncomplications, total, and low-birth weight infants.

Route of delivery. An analysis was performed to de-

Table IV. Twins: Significance of the difference between complications and no complications for cesarean section rates

	No. with cesarean section	*% with cesarean section*	*Significance level*
No complications	229	8.1	
Abruptio placentae	18	36.0	0.001
Placenta previa	21	75.0	0.001
Other hemorrhage	4	21.0	
Diabetes	3	42.8	
PROM	56	31.1	0.001
Toxemia	69	38.5	0.001
Rh incompatible	1	5.2	
Obesity	1	20.0	
ACF	66	89.1	0.001
Previous cesarean	74	97.3	0.001
Complications—total	332	43.5	0.001

termine the significance of the difference between complications and no complications for rates of cesarean section and was found to be significant at the P of <0.001 for abruptio placentae, placenta previa, premature rupture of membranes, toxemia, ACF, previous cesarean section, and total complications. These results are tabulated in Table IV.

Breakdown of the percentage of live births in comparison to the percentage of twins delivered by cesarean section in Missouri shows a statistically significant increase (P level of <0.001) in the percentage of cesarean sections utilized in the delivery of singleton and twin pregnancies over the years 1972 to 1976. Results are given in Table V.

Abnormalities of presentation. Analysis of pregnancies where at least one of the fetuses was either breech or transverse showed 30.1% of the uncomplicated patients to have an abnormal presentation and 24.2% of the complicated patients to have abnormal presentation noted for a total of 28.8%.

Further analysis of perinatal death with regard to birth order and presentation is in progress.

Effect of race, gravidity, and educational level on perinatal death and perinatal risk. The perinatal death rate by race, year, and complication showed no statistically significant data between race and presence or absence of complications (Table VI).

Risk ratios were calculated for white and nonwhite patients based on gravidity and educational level. The results of this are shown in Table VII. While this table would appear to show increased risk in white patients with less education and low gravidity, the over-all comparison of singleton and twin perinatal mortality rates, 1972 to 1976 (Table VIII), has an equally poor prognosis in twin pregnancy in white and nonwhite patients.

Table V. Percent of live births delivered by cesarean section—Missouri resident data

	1972	*1973*	*1974*	*1975*	*1976*
Cesarean sections					
Number	4,300	4,705	5,373	6,157	7,286
Percent	5.9	6.9	7.7	9.0	10.6
Twins only (%)	11.1	12.3	13.4	16.4	24.4

Table VI. Missouri twins' perinatal death rate (%) by race, complications, and year

	1972	*1973*	*1974*	*1975*	*1976*
White	10.3	9.8	13.3	10.4	11.7
Complications	26.4	17.9	27.6	22.5	19.9
No complications	7.4	7.8	9.7	6.7	9.1
Nonwhite	15.9	13.7	14.8	14.7	9.4
Complications	18.1	22.0	15.9	19.5	9.0
No complications	15.2	11.1	14.2	12.5	9.6
Over all	11.5	10.6	13.6	11.2	11.3
Complications	24.1	18.9	24.4	21.8	17.3
No complications	9.0	8.5	10.4	7.7	9.2

Comment

Approximately 1% of the pregnancies in Missouri have a marked effect on the state perinatal mortality rate by accounting for 10.10% of all the perinatal deaths in the state. This relatively infrequent occurrence (twinning) shows no difference in perinatal mortality rate with regard to race and is of significant importance to require the physicians of the state to make a concerted effort to decrease the perinatal mortality rate associated with twins. Increased patient years of education as well as increases in gravidity have a favorable predictive value for the patient with twin pregnancy; however, these still do not exclude such patients from a significant perinatal risk.

The percentage of perinatal deaths for the whole state is similar to the percentages of perinatal deaths presented in a number of other previous articles on twin pregnancy in North America, which have ranged from 9.2 to 28.6%,[1–18] with the majority accounting for 10 to 15% of perinatal deaths. Despite this fact, the occurrence of twins does not appear to significantly alarm many physicians practicing obstetrics in Missouri. The incidence of referral to major obstetric and neonatal units is low.

Complications noted prior to labor increase the perinatal mortality rate. The specific reason appears to be related to the delivery of the low-birth-weight infant in patients with premature rupture of membranes and all episodes of hemorrhage. Premature labor still accounts for the major complications, with 21.4% of patients

Table VII. Risk ratio—perinatal

White				*Nonwhite*			
Gravida	*E-11−*	*E-12*	*E-13+*	*Gravida*	*E-11−*	*E-12+*	*Grand total*
G1	14.40	12.46	8.62	G1	27.50	12.00	
G2-3	11.62	8.84	9.60	G2+	14.66	8.85	
G4+	8.16	7.55					
Total			9.51			12.1	9.90

being delivered at a gestational age of less than 36 weeks and below a mean weight of less than 2,101 grams. The delivery of the low-birth-weight infant has been felt to be the major cause of increased mortality rates in a number of other studies.[9, 12, 14–16, 18–28] The incidence of toxemia (4.9%) was less than expected in this study compared to reported ranges in several twin studies showing an incidence of 15 to 20%.[2, 5–7, 11, 13–17] It is also noted that there was no statistically significant increase in the perinatal mortality rate when toxemia was noted prior to labor. If patients who went into labor prior to 36 weeks had been excluded from the no complications analysis, however, toxemia would have shown a significant perinatal mortality rate. The perinatal birth weight for toxemia was higher than the birth weight for complications of hemorrhage, premature rupture of membranes, and premature labor, and probably accounts for the decrease in perinatal mortality rate. Those with previous cesarean section and ACF all had larger infants, with a subsequent decrease in the perinatal mortality rate.

The rising incidence of cesarean section for delivery does not appear to be decreasing the statewide perinatal mortality rate for twins. It cannot be concluded, however, that the increasing incidence of cesarean section is inappropriate. More data are needed to analyze the indications for cesarean section and the related outcome in twin pregnancy.

The major educational effort in Missouri should be directed toward the importance of twins as a major contributor to the state's perinatal mortality rate. Such education should serve to increase the early diagnosis of twin pregnancy and to facilitate consultation and referral.

Various figures have been reported in the literature with regard to the accuracy of detection of twins, varying from 50 to 95%, depending on the degree of clinical suspicion.[5–7, 22, 23, 26, 27, 30] Ultrasonic detection of early pregnancy is greater than 95% accurate[31, 32, 33] and in Sweden the use of human placental lactogen has also been reported as an effective screening method for detecting twin pregnancy.[34, 35]

The institution of a routine ultrasound screening program throughout the state available to all pregnant patients would be one of the initial steps in improving early detection. Also, aid in the evaluation of twin pregnancies at serial times for the early, attempted identification of conditions of increased risk such as mono- or diamniotic twins, abnormalities of cord insertion,[36] and dissimilar twin growth, which may lead to severe intrauterine growth retardation and preterm fetal death, is needed.[31, 37, 38] The use of serial antepartum fetal monitoring techniques should aid in the identification of these patients at increased risk for antepartum stillbirth and help clarify indications for earlier intervention.

Table VIII. Perinatal deaths/1,000 by race and number born—Missouri resident data, 1972 to 1976

	Singleton	*Twin*	*Total*
White	19.4	112.2	21.4
Black	34.4	136.9	37.3
Total	21.8	117.0	24.0

The effect of bedrest on gestational age and birth weight in multiple pregnancy has not been clearly established.[39] However, it is used by many obstetricians[4, 9, 10, 26, 27, 30] and it has been shown to increase uterine blood flow in the singleton pregnancy.[40] A recent report[33] showed a reduction in the rate of premature twin births from 48 to 27% under conditions of complete bedrest and tocolysis with a beta-mimetic if instituted between weeks 32 to 37 of pregnancy. In an effort to increase gestational age and birth weight, the state of Missouri should consider appropriate financial support to facilitate bedrest for these patients between 28 and 36 weeks, in either a home or hospital environment.

Because of intrapartum problems even in the uncomplicated cases of low-birth-weight infants, these pregnancies are best handled in select high-risk centers which have the capability of electronic fetal monitoring of both fetuses, rapid surgical intervention when indicated, and sufficient volume to be experienced in current methods of management. A perinatal review

committee should be established to evaluate perinatal death secondary to twins. The lack of referral of multiple gestations appears to be a frequent problem which contributes to the perinatal mortality rate within the state.

Conclusion

Twin gestation is a significant cause of perinatal death in Missouri. In these patients, the perinatal mortality rate is increased with the complications of premature labor, premature rupture of membranes, and episodes of hemorrhage. An educational program directed to the severity of this problem and the importance of early detection of twin pregnancy is much needed. Ultrasound detection programs and antepartum monitoring units, especially for twin pregnancy, are now being established in Missouri. Efforts to increase the birth weight and gestational age in all multiple pregnancies by establishing aid to mothers who have this diagnosis and setting up appropriate areas of delivery where physicians have sufficient experience and volume to adequately handle the obstetric and neonatal complications that occur in multiple pregnancy are indicated. A perinatal committee on twin pregnancies needs to be established to stimulate the development of referral patterns for the management of such patients.

The occurrence of multiple pregnancy has often been regarded as a rarity and a condition which physicians have often not viewed seriously. The information gained from this study on the high percentage of perinatal deaths generated from a relatively low number of twin births should call attention to the seriousness of this problem. Twin pregnancy demands a concentrated effort with new approaches in an attempt to lessen the potential fetal wastage from such a condition.

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Discussion

DR. CHARLES E. GIBBS, San Antonio, Texas. An organized attack on perinatal death must begin with accurate information about those factors associated with death as well as specific causes of death in the population to be cared for. For example, multiple gestation is a factor associated with an increased perinatal mortality rate and the deaths are usually due to RDS, labor hypoxia, intrauterine fetal transfusion, etc. Dr. Medearis and his group have presented us with data regarding perinatal death associated in a general way with twinning. Naeye and associates[1] recently published some material regarding the probable causes of death in a large number of twins. Both approaches are useful.

The role that multiple gestation plays in perinatal death varies from population to population. The authors found that rates did not vary with race and this is somewhat surprising with the increased frequency of fraternal twinning in black women. This might be explained by the finding of Naeye and associates that monozygotic twins suffered a mortality rate 2.7 times that of the dizygotic infants. In our hospital, in a recent 5 year period, multiple gestation was associated with only 6% of the perinatal deaths, whereas Drs. Medearis and Jonas and their group reports a 10% figure. One possible reason for the difference might be that all of our liveborn infants were managed by neonatologists in a very good Level III nursery as contrasted to the Missouri experience, which includes all types of care. Dr. Naeye reported that Addis Ababa twins had 2.5 times the mortality rate of a study group in the United States. The causes of death were similar but more deaths from intrauterine infection and abruptio placentae were noted. It is my impression that in the United States RDS is the leading cause of death associated with multiple gestation. Dr. Jonas indicated that multiple gestation requires early diagnosis and good prenatal care followed by an experienced and sophisticated environment for delivery. We agree and believe that with such care a realistic goal for a perinatal mortality rate associated with multiple gestation is 50/1,000 births and that these deaths would make up less than 5% of the total perinatal deaths.

I was interested in the information that abruptio placentae was associated with 49 of the 835 deaths, an involvement rate of 0.6%. It was surprising that more of these deaths were neonatal (28) than were fetal (21). It is probably safe to say that RDS was the killer and that the foregoing premature birth was triggered by the abruptio placentae. If this is true, one could expect a reduction in perinatal loss associated with abruptio placentae through improved neonatal care, even before the cause and prevention of the condition are identified.

Finally, I would like to comment on data derived from birth certificates, fetal death certificates, and death certificates. One has only to consider how carelessly and quickly these documents are completed by many of us to begin to question their accuracy. In Texas (and, I think, elsewhere) it is very likely that much of the clinical information (cause of death, duration and complications of pregnancy, month beginning prenatal care, etc.) is inaccurate and therefore unreliable for any scientific purpose. On the other hand, the demographic information (place of residence, place of birth, birth order, sex and birth weight, education and occupation of parents) is usually correct and therefore useful. If regional planning by Health Systems Agencies continues these data will be very helpful for planning and evaluation.

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DR. HOWARD G. MCQUARRIE, Salt Lake City, Utah. Drs. Medearis and Jonas and their associates, utilizing retrospective computer analysis of information gleaned from birth certificates, have addressed the incidence and perinatal outcome of twinning in Missouri, comparing the study results with an appropriate array of published material.

The paper reflects a sincere effort to unmask the elusive key to improvement of perinatal outcome in twin pregnancy by the computer study of vital statistics. The paper did not unveil new or innovative ideas but did reinforce the importance of early diagnosis and the ominous complications possible in twin pregnancy, and offered regional planning, consultation, and referral as logical steps to improve the outcome.

The study's documented references, plus the contribution by Harris and Gibbs,[1] does suggest that early diagnosis of twinning is essential and may be possible by simple clinical measurement of the uterine growth or more sophisticatedly by ultrasound or x-ray.

Early diagnosis allows timely inventory of resources available to assess and treat predictably the problems of twinning. The simple availability of an extra pair of trained hands on site at delivery has improved the outcome of the delivery process in our practice.

Whether or not it is practical in a known twin pregnancy to change the environment of the mother to a regional center to enhance rest and give nutritional and educational counseling away from her home exposes a current controversy that will be worthy of exploration.

This observer senses that the patient who is at bed rest opposes centralization of care, subspecialization, and the resulting fragmentation of care with the end result of depersonalization so much that house calls for prenatal management of twins are in vogue in our practice.

Twinning, by all styles of analysis, presents the obstetrician with unique problems, difficult decisions, and often clinically nonpredictable challenges that are worsened by "Surprise! It's twins!"

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DR. JOHN F. HUDDLESTON, Birmingham, Alabama. I am certainly a proponent of the regionalization of perinatal care. However, residing in a rural state with considerable distances between primary care and referral facilities, I question whether maternal transfer will prove to be of great value in avoiding perinatal deaths associated with twinning.

In the first place, as Dr. Jonas has pointed out, the perinatal deaths are primarily due to prematurity associated with premature labor and with antepartum hemorrhage. The active phase of premature labor is notoriously rapid. Intravenous tocolytic agents probably cannot be safely administered inside an emergency vehicle speeding down the highway. A gravida with an actively bleeding placenta previa is likewise hardly a candidate for safe transfer over any great distance.

Second, even if we become proficient at the early identification of twin pregnancies, their prophylactic referral during the third trimester for observation and domiciliary care is of questionable benefit,[1] is quite expensive, and may cause considerable family turmoil.

Taken together, these factors cast some doubts on the ability of in utero referrals to have significant impact on the perinatal mortality rate in twin pregnancy.

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DR. WILLIAM B. STROMME, Edina, Minnesota. As late as 25 years ago Prof. Will Nixon of the University of London established a policy there of bed rest from 32 to 36 weeks of multiple pregnancy and felt that this was a principal factor in reducing the perinatal mortality rate.

Also, because of the concerns of premature delivery in multiple pregnancy, we should be mindful of the fact that many of these people have silent incompetent cervix. This should be looked for and corrected when found.

DR. DONALD L. CLINE, Indianapolis, Indiana. I feel that with the increasing use of Clomid and Pergonal we are going to encounter more frequent multiple gestations.

I would like to offer two suggestions for consideration: (1) the prophylactic use of cervical circlage in multiple gestations could be considered if the multiple pregnancy is diagnosed early and (2) the prophylactic use of beta-methasone at an appropriate time in a multiple gestation may be indicated. These two factors may very well reduce prematurity as a result of silent cervical dilatation and, if a premature delivery does occur, the survival rate might be increased with the use of beta-methasone.

DR. WILLIAM P. GIDEON, Tulsa, Oklahoma. In light of the decrease in the perinatal mortality rate in domiciliary type institutions, this might be an opportune time in light of the current controversy on overbedding in many of our hospitals to start a drive to establish long-term care units at a reduced price per diem. It is my understanding that in certain cities in the Southwest now, specifically Dallas, there is a program where the average daily cost for a bed is around $35 or $37 a day. This would be much more economical than the cost in a neonatal intensive-care unit.

DR. GERALD B. HOLZMAN, East Lansing, Michigan. Although I agree with the authors that it is desirable to make the diagnosis of a twin pregnancy early, the employment of ultrasound in every pregnancy seems a bit excessive. Most of us do not have units in our office and the hospital charge for this procedure is not insignificant. Twinning does increase with advanced maternal age. Thus, one might consider these women to be sufficiently at risk to justify an ultrasound examination, particularly since many of them will consent to an early midtrimester diagnostic amniocentesis to rule out a chromosomal abnormality.

DR. MEDEARIS (Closing). Dr. Gibbs' comment on the difference of race in our study is reflected by the percentage incidence of pregnancies in black patients in Missouri, and by the fact that the perinatal mortality rate in nonwhite patients has markedly decreased over

a 2 year period of time. This probably is related to the availability of abortions to this patient population, and this occurrence toward the end of our 5 year period alters our statistics regarding black patients. It will be interesting to see if recent funding decisions on abortion influence our perinatal mortality rate in the nonwhite patients.

I agree with the problems of data collection from birth certificates; in many cases we had to further hand sort and inquire to complete our files. One of the areas that was particularly frustrating was presentation. Physicians tend in twin pregnancies to list either vertex-vertex, breech-breech, or transverse-transverse. It would seem, from looking over all the data, they do not accurately describe the presentation of the twins. This is a major problem in pursuing data. I would like to encourage people to fill out these forms accurately.

With regard to Dr. McQuarrie's comments, we really had not advocated that the patient necessarily be away from home. We have encouraged the state to offer aid to these patients so that they might be allowed to stay at bed rest or reduced activity at home. We have been interested in comparing one group in a domiciliary facility as opposed to a group that is at bed rest at home.

Last, I would like to comment on the question of referral of multiple pregnancy. The problem in the state appears to be not necessarily the referral and transfer to a high-risk facility of a patient who is unstable but, in many cases of a known diagnosis of multiple pregnancy, the insistence of physicians on keeping this pregnant patient in their community.

I would cite a recent episode where a physician whose patient was known to have a set of triplets had consulted one of the obstetric staff and a neonatologist at one of the referral centers approximately a month prior, and told them of his awareness of multiple pregnancy. He then proceeded, when this patient was in early labor, at approximately 28 to 30 weeks, to deliver her at his institution because triplets had never been born in that town, and he desired to deliver them there. At the time the neonatologist arrived, rather hurriedly, after approximately 50 to 60 miles by ambulance, he found all infants intubated, two in the esophagus, all being ventilated with adult equipment. All three fetuses have now been born, and are now buried in that town. I think that is one of our major concerns about multiple pregnancy.

Information for authors

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Ultrasonic evaluation of the fetal heart

A report of experience and anatomic correlation

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Identification of fetal intracardiac structures in utero is accomplished with B-scan, gray-scale ultrasonography. Sagittal and transverse ultrasonographs of the interventricular septum, aortic root, tricuspid, and mitral valves are presented. These structures are characterized with respect to their relations to each other, atrial and ventricular chambers, and acoustic appearances. Correlation of these cardiac structures is made with gross anatomic fetal specimens sectioned in longitudinal and transverse planes. Recognition of fetal intracardiac detail may be of aid in future noninvasive investigations of human fetal cardiovascular dynamics. (AM. J. OBSTET. GYNECOL. 134:422, 1979.)

PULSE-ECHO A-mode, time-motion (T-M) mode and Doppler ultrasound techniques have been used in obstetrics to detect the presence of fetal heart activity in confirming fetal viability.[1-6] However, few studies have been reported with B-scan techniques to study the anatomy of the fetal heart in utero. Early B-scan studies of fetal cardiac anatomy have been performed with bistable technique. Some fetal intracardiac details may not be generated by bistable technique if their reflected echo intensities are lower than the threshold echo intensities detected by the given ultrasound system.

Such bistable scans have revealed that the cardiac interventricular septum can be identified within a circular transonic structure within the fetal thorax.[7, 8] The ultrasonic representation of atrioventricular valves was also reported.[9] In a report by Egeblad, Bang, and Nonheved,[10] bistable imaging of a fetal intracardiac structure identified as the "atrioventricular septum" was made. They stated that such a septum includes the area of the tricuspid and mitral valves and their immediate supporting structures. Egeblad and associates also tentatively identified fetal atria, ventricles, interventricular and interatrial septa, pulmonary conus and artery, aortic root, and superior and inferior venae cavae on the basis of their relationships to the "atrioventricular septum."

Recent ultrasound tomographic studies of fetal anatomy have used gray-scale techniques. Kossoff[11] reported that fetal heart chambers may be delineated from myocardium. Flanigan and Buttny,[12] using a slow, single-pass technique in obtaining gray-scale B-scans of the fetal heart, reported the interventricular septum as a wavy structure within a transonic area in the center of the fetal thorax. In March, 1975,[13] we reported on the sonographic appearance of a fetal cardiovascular sonographic image display which we believe to be the fetal aortic root as it exists from the left ventricle and ascending aorta.

The present communication is a report of the continuation of work on the sonographic imaging of the fetal cardiovascular system by B-scanning, gray-scale techniques with the tentative identification of other fetal intracardiac structures.

Materials and methods

A Unirad Sonograf II with Greatone Zoom Display capability was used in the investigation. This diagnostic pulse-echo unit was equipped with simultaneous A-and B-mode display modules and T-M mode capability. An electronic caliper module to measure quickly fetal biparietal diameters was also available.

A 2.25 MHz multipurpose long-focus transducer of

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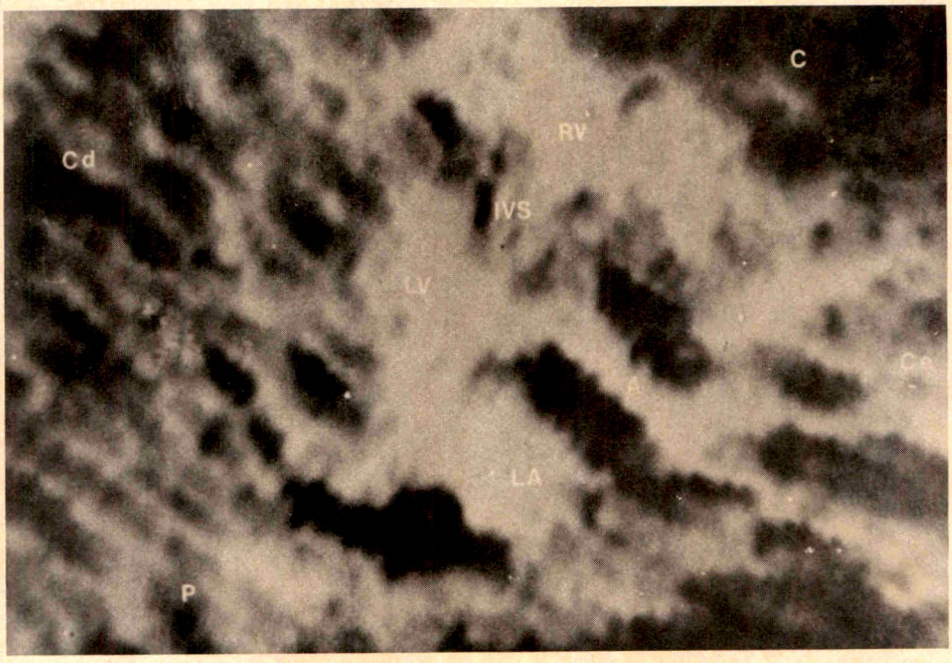


Fig. 1. Sagittal B-scan of the heart in a fetus at 40 weeks of gestation. The walls of the aortic root *(A)* appear as two dark, parallel echoes. The anterior wall of the aortic root is continuous with a lighter gray band of echoes which divides the sonolucent cavity into two chambers. This lighter gray band of echoes is the interventricular septum *(IVS)*. The sonolucent chamber anterior to the interventricular septum is the right ventricle *(RV)*. The sonolucent chamber posterior to the interventricular septum is the left ventricle *(LV)*. A small gray echo appears as an appendage to the posterior wall of the aortic root. This echo may be part of the anterior leaflet of the mitral valve. Hence the left atrium *(LA)* can be identified. Cephalad *(Ce)*, caudad (Cd), fetal anterior chest wall *(C)*, posterior aspect of the fetus *(P)*.

13 mm diameter and a 3.5 MHz 19 mm diameter transducer focused at 7 to 11 cm were used.

Mineral oil or aqueous gel was used as a coupling agent between the transducer and abdominal skin for optimal sound transmission.

Fresh-frozen and formalin-fixed anatomic specimens for correlative study were obtained from the embryologic collection of the Department of Pathology, Charity Hospital of Louisiana at New Orleans. Longitudinal and transverse sections of these fetal specimens were made with a band saw or a brain knife.

Patients in their third trimester referred for obstetric ultrasound were examined for determination of fetal intrauterine attitude, estimation of gestational age by biparietal diameter, and placental localization. Fetal heart examinations were accomplished after the routine obstetric ultrasonic examination and required approximately 30 extra minutes of scanning time.

The position and presentation of the fetus were ascertained by B-scan to localize the fetal thorax and heart. Fetal heart activity was then confirmed by A-mode and/or T-M mode. The fetal heart was serially examined by longitudinal and transverse scans in 0.5 to 1.0 cm sections. A slow, single pass of the transducer over the area of the fetal heart was used to demonstrate any oscillations within the fetal heart space. In some patients the position of the fetus was such that it was difficult to locate the fetal heart with B- and A-modes alone. A Doppler unit was then found to be helpful in audibly identifying the fetal heart. Such a maneuver enabled one to reposition the B-scanning transducer for correct angulation in order to obtain the required longitudinal or transverse sections of the fetal heart. All B-mode ultrasonographs were recorded on 35 mm and/or Polaroid film.

Results

Approximate sagittal ultrasonographic sections of an in utero fetus at 40 weeks' gestational age are presented in Figs. 1 and 2. The dark gray to black areas in the ultrasonographs represent sonic interfaces. The lighter areas or sonolucent parts of the ultrasonographs represent homogeneous fluid areas. Two dark, parallel sonic interfaces appear to arise from a sonolucent saccular area caudal to these interfaces. Generally, a zigzag image of the parallel interfaces can be seen. An inter-

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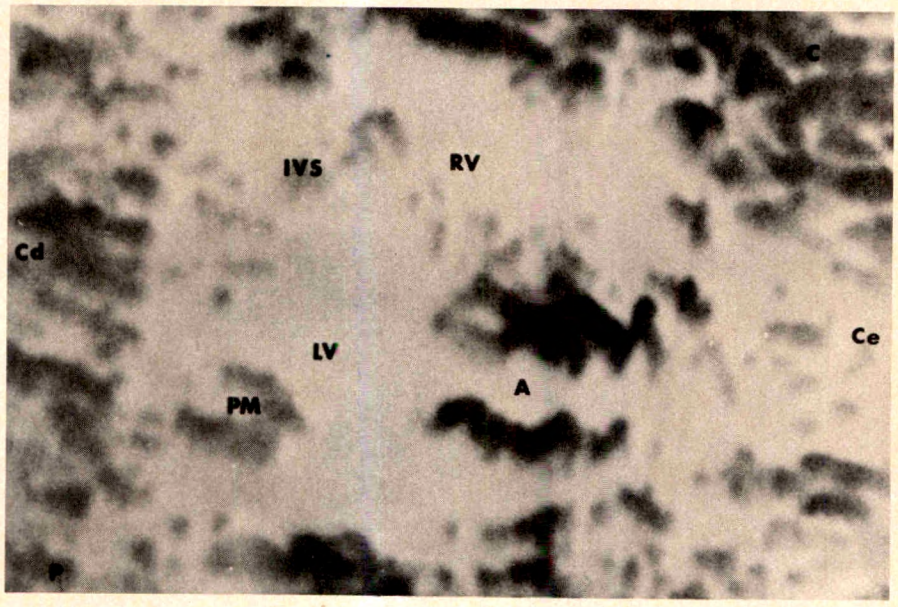


Fig. 2. Sagittal B-scan of the heart in a fetus at 40 weeks of gestation. The walls of the aortic root *(A)* are apparent as two dark, parallel echoes. The anterior wall of the aortic root is continuous with the interventricular septum *(IVS)*, which appears as a set of lighter gray echoes with a wavy appearance. A gray echo seems to jut into the sonolucent space posterior to the interventricular septum. This echo may represent a papillary muscle *(PM)*. The right ventricle *(RV)* and left ventricle *(LV)* are identified. Cephalad *(Ce)*, caudad *(Cd)*, fetal anterior chest wall *(C)*, posterior aspect of fetus *(P)*.

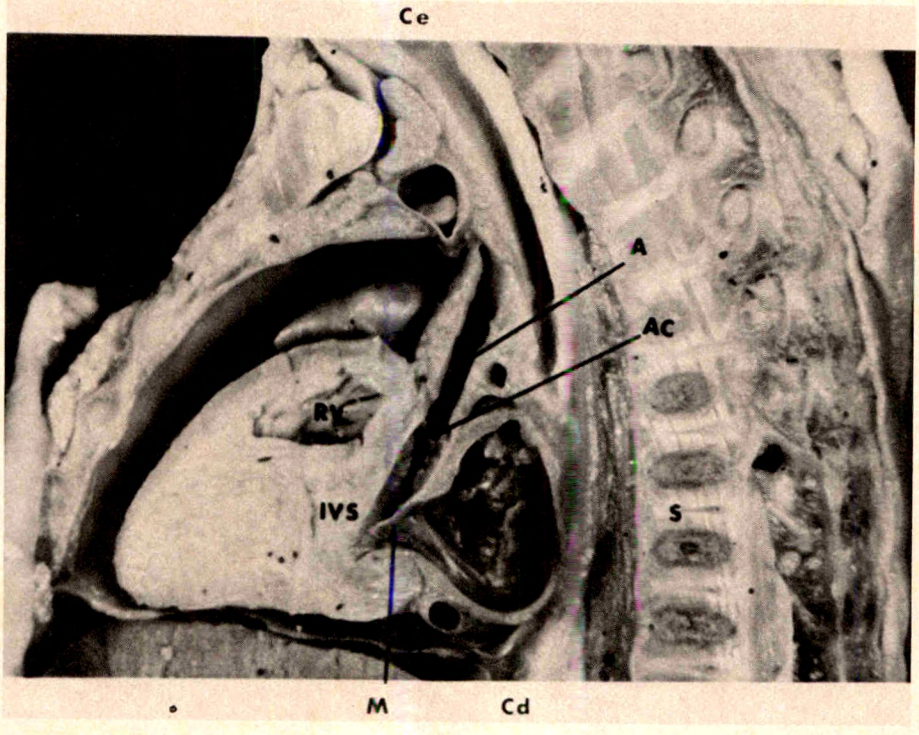


Fig. 3. Sagittal section through the heart in a morbid fetus at approximately 19 weeks of gestation. The aortic root *(A)* is clearly visualized. Part of the aortic valve is also apparent *(AC)*. The interventricular septum *(IVS)* is continuous with the anterior wall of the aorta. The anterior leaflet of the mitral valve *(M)* is continuous with the posterior wall of the aortic root. The right ventricle *(RV)* and the left atrium *(LA)* are apparent. The left ventricle has been cut away in this section. Cephalad *(Ce)*, caudad *(Cd)*, fetal anterior chest wall *(C)*, fetal spine *(S)*.

face that is lighter in appearance than these parallel interfaces is continuous with the more anterior of the two parallel interfaces and continues to the caudal extent of the sonolucent cavity to divide the cavity into anterior and posterior chambers. The waviness of such an interface imparts the impression of motion. Another gray interface can be seen as a small appendage to the caudal extent of the more posterior of the two dark, parallel interfaces in Figs. 1 and 2.

Correlation of the anatomic source of the interfaces represented on the ultrasonographs was done from morbid fetuses sectioned slightly oblique to the sagittal plane. Fig. 3 shows a 19-week-old fetus sectioned in approximately the same plane in which the ultrasonographs in Figs. 1 and 2 were made. The two dark, parallel interfaces present in the ultrasonographs appear to originate from the anterior and posterior aortic root wall/blood interfaces. The gray interface continuous with the anterior aortic root wall may represent the interventricular septum. The appendicular interface continuous with the posterior aortic root wall may represent parts of the anterior leaflet of the mitral valve. Once the basic landmarks of aorta, interventricular septum, and mitral valve are identified, the left ventricle, right ventricle, and left atrial cavities can also be identified as shown in Figs. 1 and 2. In Fig. 2 a gray interface appears to jut into the left ventricular cavity and is continuous with the echoes from the posterior left ventricular wall. Such an interface may be a papillary muscle. Fig. 4 shows the orientation of the heart in the fetal thorax, and the intracardiac structures identified can be compared with those shown in Figs. 1 and 2.

Fig. 5 is an approximate sagittal B-scan of an in utero fetal heart at 37 weeks' gestational age. Oscillations are present within the sonolucent fetal heart cavity. Two dark, parallel interfaces are present and again these probably represent anterior and posterior aortic root wall/blood interfaces. The anterior aortic root wall appears to be continuous with a set of echoes stretching to the caudal extent of the fetal heart space. These echoes may originate from the interventricular septum/blood interface. Spiking oscillatory echoes appear to be either continuous or contiguous with the anterior aortic root wall. These probably arise from parts of the tricuspid valve. The posterior aortic root wall is continuous with another set of oscillatory echoes that extend into an echo-free cavity. It is likely that these echoes arise from the anterior leaflet of the mitral valve. Hence right and left ventricles may also be identified in Fig. 5. The structures identified in Fig. 5 can be compared with the intracardiac structures labeled in Fig. 6.

Fig. 7 is an approximate transverse or cross-sectional ultrasonograph of an in utero fetal heart at 40 weeks' gestational age. Two dark, parallel echoes appear in a more sonolucent space bordered by darker echoes. Grayer echoes originate from both parallel echoes. Correlation of the echo patterns with morbid fetal cross-sectional cardiac anatomy (Fig. 8) shows that the two dark, parallel echoes probably originate from the aortic root wall/blood interfaces. Echoes continuous with the left anterior portion of the aortic wall may arise from the interventricular septum and the zigzag echoes from the left posterior portion of the aortic root may arise from the anterior leaflet of the mitral valve. The sonolucent area anterior to the aortic root may be the right ventricular outflow tract and the sonolucent area behind the aortic root may be the left atrium. Hence the limits of the left ventricle may be delineated by the interventricular septum anteriorly and the mitral valve posteromedially, as shown in Fig. 7. The transverse section of the fetal heart shown in Fig. 9 can be compared with the ultrasonograph of the fetal heart in Fig. 7.

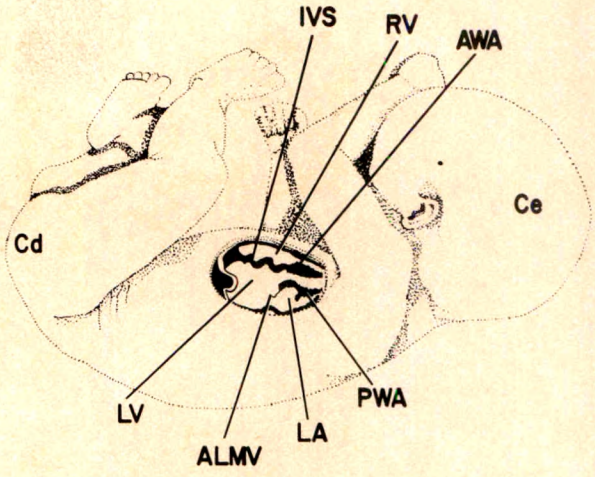


Fig. 4. Schematic representation of an approximate sagittal section of the fetal heart in the fetal thorax. The interventricular septum *(IVS)*, right ventricle *(RV)*, anterior wall of the aortic root *(AWA)*, posterior wall of the aortic root *(PWA)*, left atrium *(LA)*, anterior leaflet of the mitral valve *(ALMV)*, and the left ventricle *(LV)* are labeled. Cephalad *(Ce)*, caudad *(Cd)*.

Comment

The present B-scan gray-scale studies of fetal hearts in sagittal and transverse sections demonstrated that fetal intracardiac structures can be identified. Fetal heart visualization was best accomplished from approximately 35 weeks of gestation through term due to the large size of the fetal heart with respect to the fetal thorax and the minimal amount of positional change of the fetus. In general the basic intracardiac landmarks used to orient the examiner to the various cardiac chambers were the anterior and posterior walls of the

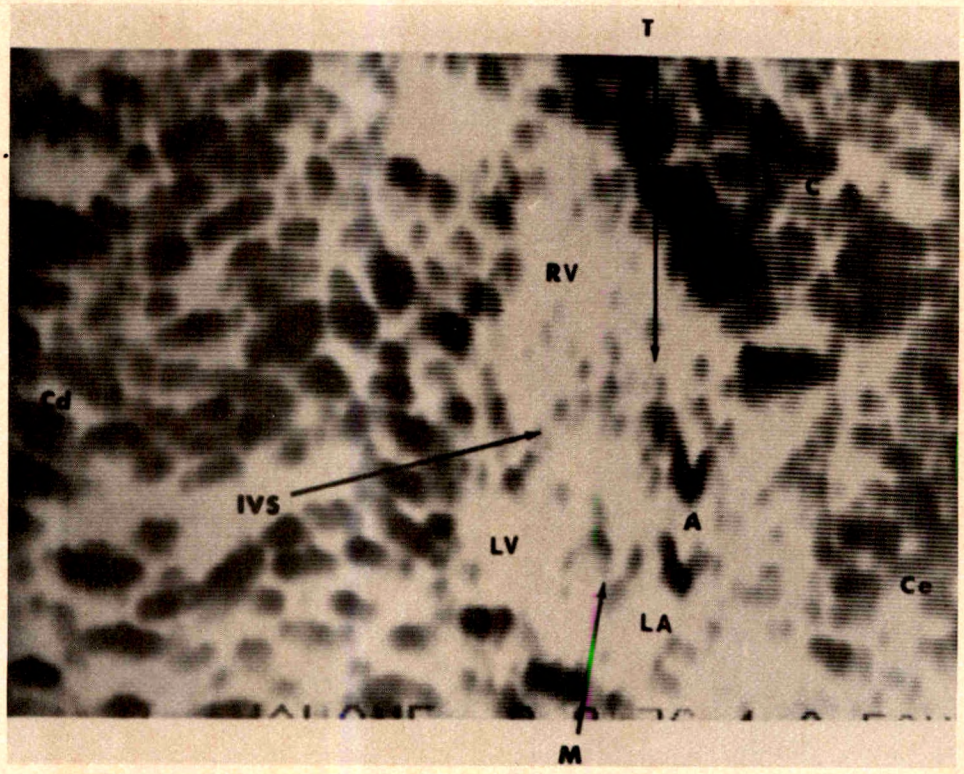


Fig. 5. Sagittal B-scan of heart in a fetus at 37 weeks of gestation. The walls of the aortic root *(A)* are apparent as two dark, parallel echoes. A lighter gray echo continuous with the anterior wall of the aortic root is the interventricular septum *(IVS)*. A lighter gray echo continuous with the posterior wall of the aortic root is the anterior leaflet of the mitral valve *(M)*. A tricuspid valve leaflet *(T)* appears as sharp spiked echoes contiguous with the anterior wall of the aortic root. The right ventricle *(RV)*, left ventricle *(LV)*, and left atrium *(LA)* are identified. Cephalad *(Ce)*, caudad *(Cd)*, anterior chest wall of fetus *(C)*.

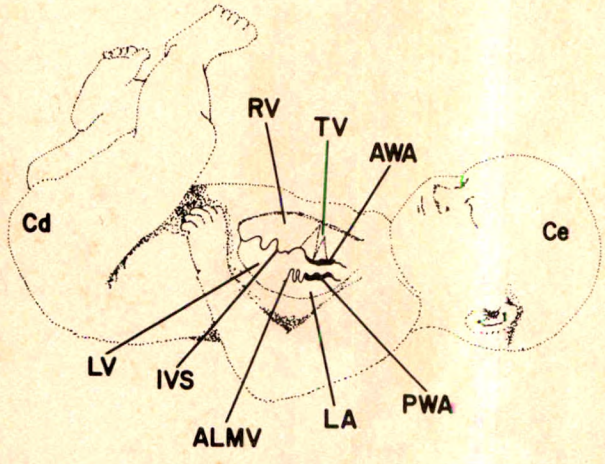


Fig. 6. Schematic representation of an approximate sagittal section of the fetal heart of the fetal thorax. The interventricular septum *(IVS)*, left ventricle *(LV)*, right ventricle *(RV)*, anterior leaflet of the mitral valve *(ALMV)*, left atrium *(LA)*, anterior wall of the aortic root *(AWA)*, and posterior wall of the aortic root *(PWA)* are labeled. Slight positional change of the fetus from that shown in Fig. 4 allows one to visualize parts of the tricuspid valve *(TV)*. Cephalad *(Ce)*, caudad *(Cd)*.

aortic root, the interventricular septum, the anterior leaflet of the mitral valve, and parts of the tricuspid valve. In this particular study, the walls of the aortic root were structures that tended to be characterized by high-intensity or darker interfaces, whereas the interventricular septum and atrioventricular valves were sonographically demonstrated as lower intensity or lighter gray echoes. Such differences in reflected echo intensities may be a function of the histologic composition of these cardiovascular structures, the angle of incidence of the pulsed ultrasonic beam to the interface being examined, or both of these factors.

The atrioventricular valves are thin and composed of delicate connective tissue with an acoustic impedance only slightly different from that of blood. Thus the atrioventricular valves may not reflect as much ultrasound as do the aortic walls, which are composed of denser elastic and fibrous connective tissues and smooth muscle. The acoustical impedance mismatch between the aortic walls and blood may be large enough to give the reflected ultrasound a higher in-

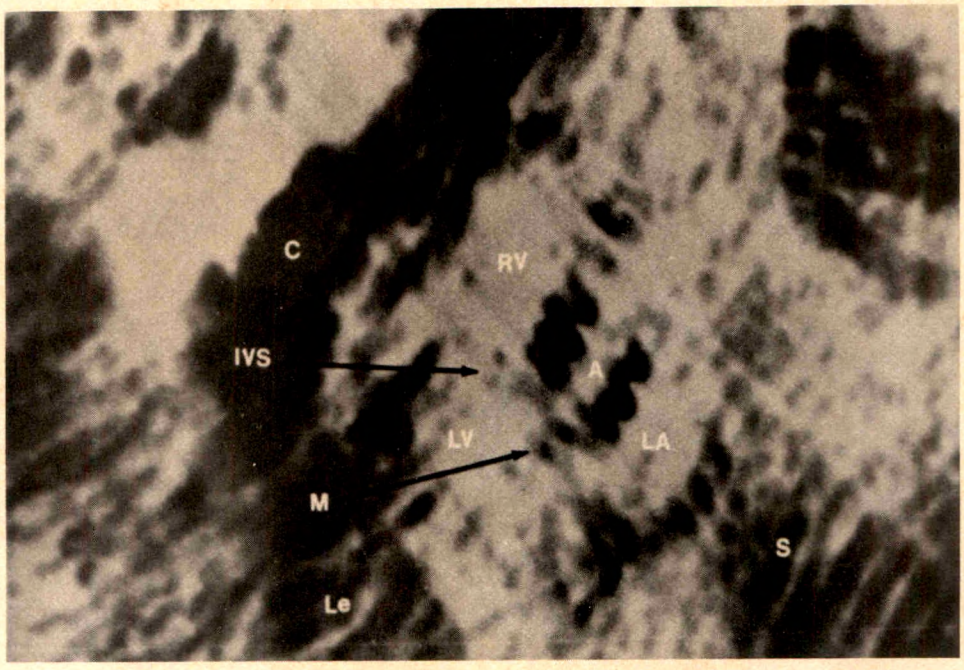


Fig. 7. Transverse B-scan of the heart in a fetus at 37.4 weeks of gestation: View of the aortic root. The walls of the aortic root *(A)* appear as two dark, parallel echoes within a sonolucent cavity. The anterior wall of the aortic root is continuous with lighter gray echoes of the interventricular septum *(IVS)*. The posterior wall of the aorta is continuous with lighter gray zigzag echoes from the anterior leaflet of the mitral valve *(M)*. The right ventricle *(RV)*, left ventricle *(LV)*, and left atrium *(LA)* are noted. Fetal anterior chest wall *(C)*, fetal spine *(S)*, left side of fetus *(Le)*.

tensity. Similarly, a well-vascularized muscular interventricular septum may present with an acoustical impedance slightly different from that of blood, the difference being due to the cardiac muscle of the interventricular septum. The membranous part of the interventricular septum may also tend to give a sonographic representation similar to that of the atrioventricular valves since it too is composed of connective tissue within an endothelial lining.

It is known that as the angle of incidence of the pulsed ultrasound to the tissue interface being studied approaches 90 degrees, the amount of reflected ultrasound detected by the ultrasonic receiver approaches a maximum.[14] Perhaps the anatomic position of the aortic root with respect to the movement of the transducer position was such that the aortic root generally presented a near normal interface to the incident ultrasonic beam of the transducer in which maximal reflected ultrasound could be detected. Conversely, the positions of the interventricular septum and atrioventricular valves may have presented a less favorable lie to the incident ultrasonic beam for the maximization of the reflected echoes from such interfaces. We feel that both of the above-mentioned factors play a role in the sonographic appearances of the described fetal cardiac structures.

Some problems in correlating B-scan fetal cardiac anatomy to the cardiac structures of the morbid fetal specimens were due to slight obliqueness of the ultrasonic tomographs of the fetal heart with respect to the sections cut in the morbid specimens. True sagittal or transverse sections were not easy to obtain in all fetuses studied. Slight obliqueness of the B-scans of the heart may add a degree of distortion that results in less commonly recognizable relationships of intracardiac structures and chambers. Also it must be noted that the hearts of the morbid specimens studied for correlation appeared to be fixed in ventricular systole so that ventricular chamber sizes could not be very well appreciated.

In general it was observed that B-scan cross-sections of the aortic root of the fetal heart did not appear circular but the walls appeared to be more or less parallel to each other. Usually the lateral margins of the aortic root did not fill in or show a wall/blood interface. This was probably due to the incident ultrasonic beam being parallel to the reflecting interface. This artifact may be corrected by angling the transducer so that the incident beam strikes all aspects of the aortic root wall/blood interface at an angle as close to 90 degrees as possible.

Added confirmation of the fetal cardiac structures

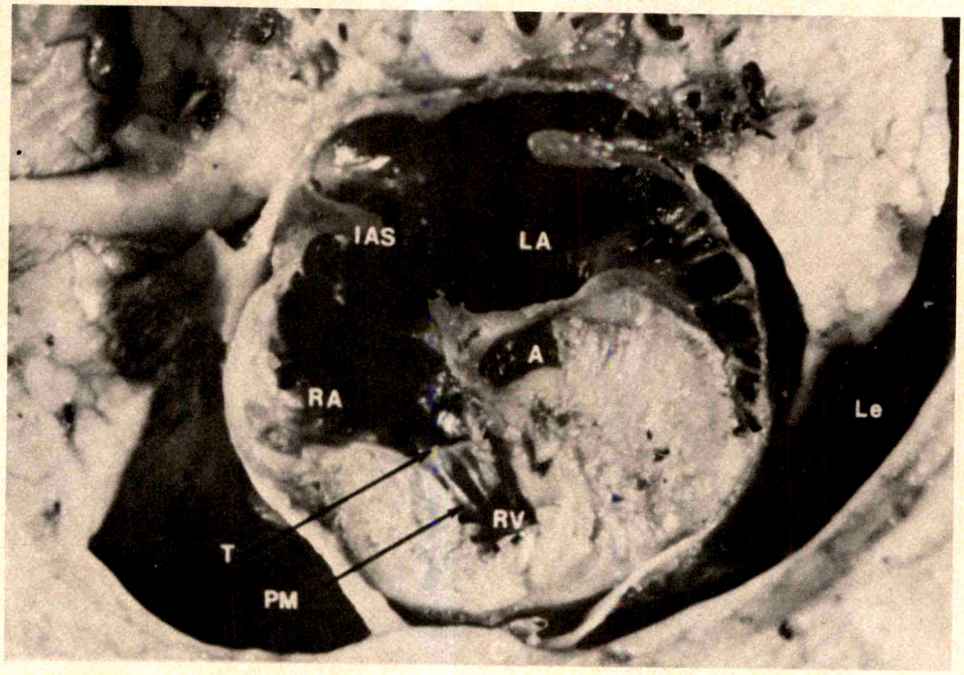


Fig. 8. Cross-section through the level of the heart in a morbid fetus at approximately 25 weeks of gestation. The right and left atria *(RA* and *LA*, respectively) appear quite prominent relative to the total area of the heart. The tricuspid valve *(T)* and attaching papillary muscles *(PM)* are apparent within the right ventricle *(RV)*. Part of the interventricular septum *(IVS)* and aortic root *(A)* are also visible. Part of the interatrial septum *(IAS)* has been torn away. Anterior chest wall *(C)*, posterior aspect of fetus *(P)*, left side of fetus *(Le)*.

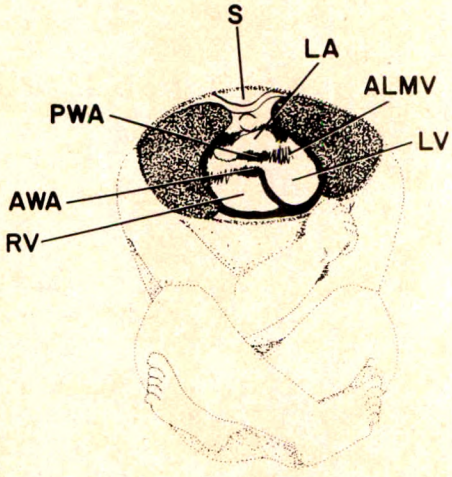


Fig. 9. Schematic representation of a transverse section of the fetal heart in the fetal thorax. The anterior wall of the aortic root *(AWA)*, posterior wall of the aortic root *(PWA)*, anterior leaflet of the mitral valve *(ALMV)*, left atrium *(LA)*, left ventricle *(LV)*, right ventricle *(RV)*, and interventricular septum *(IVS)* are labeled. Fetal spine *(S)*.

delineated by B-scan was accomplished by T-M mode scanning, as was done in our previous work[13] and that of Winsberg.[15] Such T-M mode fetal heart work will be the subject of a subsequent report.

In summary, we have expanded on our experience with ultrasonic visualization of fetal cardiovascular structure. Gray-scale ultrasound aids one's attempt to identify the various fetal intracardiac structures by both their echogenic properties and their anatomic relations. Identification of motion by such intracardiac structures can be of assistance in recognizing fetal viability with B-scan technique alone. Consistent recognition of fetal cardiovascular structures by both B-scans and T-M mode tracings may enhance the possibility for the assessment of fetal cardiovascular physiologic function by fetal echocardiography.

Present technologic advances in measuring blood velocity by a pulsed Doppler system has combined pulsed Doppler instrumentation with the real-time visualization of the vessels in which such blood velocity is measured in order to quantitate blood flow.[16] Pulsed Doppler ultrasound in combination with T-M mode echocardiography is also presently used to evaluate murmurs due to turbulent flow in congenitally malformed hearts in pediatric patients.[17]

Structural recognition of fetal intracardiac anatomy by B-scan is thus the initial step in investigations of fetal blood flow and cardiac output and may eventually prove to be of value in the diagnosis of congenital heart

disease in utero or in evaluating the cardiovascular status of the fetus in various pathologic processes in pregnancy, such as maternal diabetes and hypertensive disease.

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Discussion

DR. JOSEPH C. SCOTT, JR., Omaha, Nebraska. This report of in utero identification of fetal cardiac structure is an extension of the authors' report presented before this Association in 1975. The reality of these studies ultimately will be a finer understanding of human in utero cardiac function, development, and anomalies.

Since the early development of clinical ultrasound, the technology has advanced at a steady pace. Pelvic sonography has proved itself as a useful adjunct clinically. Pulsed ultrasound, because it is noninvasive and considered safe, is forging new understandings of both placental and fetal development. As the technology continues to be refined, our generation will undoubtedly see ultrasound replace more invasive techniques for fetal and placental evaluation and the identification of anomalies.

Real-time scanning of the fetal heart presents a few challenges that adult heart scanning has not had as problem areas. Orientation of the fetal thorax and its contents varies with gestation and the fetal presentation. If there is motion, a change in orientation of the ultrasound plane occurs. The fetal heart is pumping at a greater pace than adult hearts and thus study of wall thickness and valve motion is more challenging. Superior camera, film, and/or videotape capability is a must to obtain good records. Also, simultaneous electrocardiogram tracings in conjunction with the TM mode ultrasound scanning may be of marked assistance in pinpointing valvular function in the fetus.

I would like to ask the authors to speculate the future directions of their studies and also would be interested in knowing what their experience has taught about the major equipment difficulties they have encountered.

DR. CHARLES C. BIRD, Evanston, Illinois. Ultrasound has been an extremely valuable diagnostic adjunct in the Department of Obstetrics and Gynecology at Evanston Hospital for several years, and with the addition of real-time ultrasonography the use of this test has expanded incredibly. We are so thrilled with it that it is actually hard to imagine in many instances practicing obstetrics without it. The portability, simplicity, and noninvasiveness of ultrasound allow the clinician to easily assess fetal age, position, and viability as well as placental location with minimal effort and virtually no patient risk. The enormous benefits are obvious.

As is true with any new technique, more and more refinements in technology lead to enhanced interpretation of results. The increased expertise of those who work with ultrasound can be no more clearly demonstrated than by the work of Yamaguchi and Lee. In 1975 at the annual meeting of the Central Association of Obstetricians and Gynecologists these authors[1] presented some preliminary data relating to the ultrasonographic identification and evaluation of the fetal heart, using a compound B-scan diagnostic unit with gray-scale processing. Today we have seen an impressive pictorial display clarifying, solidifying, and extending their efforts. Whereas their first report dealt with the identification of the fetal heart in general, i.e., the "fetal cardiac silhouette sign" and the aortic root, now their work has expanded to consistently demonstrate smaller and more subtle intracardiac structures. The

authors, using exquisite gross anatomic correlation with morbid fetal hearts, present convincing evidence that they can clearly delineate, using ultrasound, the fetal cardiac root, interventricular septum, and tricuspid and mitral valves.

The literature demonstrates that although in instances of congenital heart disease there is no significant increase in fetal distress in labor, no increase in the cesarean section rate, and no increase in maternal prenatal complications, antenatal detection of this fetal problem is very helpful in predicting small-for-dates infants.[2] The enormous pediatric benefit of foreknowledge of this complication, i.e., congenital heart disease in utero, is clear.

With only the data we have seen today, I can envision the in utero diagnosis of hypoplasia of the left ventricle, significant ventricular septal defects, aortic stenosis, tetralogy of Fallot, tricuspid atresia, and possibly coarctation of the aorta, to mention a few. The next logical step, of course, would be the transfer of mothers carrying fetuses afflicted with congenital heart disease to larger centers where appropriate postpartum neonatal management would be effected.

I have two principal questions to ask the authors: (1) Have any instances of congenital heart disease been discovered and, if so, was there, possibly, surgical confirmation of the ultrasonographic interpretation? (2) Is this a technique that can be reasonably easily reproduced by more inexperienced ultrasonographers or, in other words, at the present time, is this a practical procedure?

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DR. YAMAGUCHI (Closing). With respect to Dr. Scott's question on the future direction of our laboratory, we do hope to present more studies relating to echocardiographic observations of the fetal heart at a later date. As has been evident from the literature, invasive studies on fetal cardiovascular physiology have been done solely on animal models such as sheep. Using the data derived from our present study of fetal cardiac anatomy and combining it with refined real-time ultrasonographic techniques to observe cardiac dynamics and the application of pulsed Doppler ultrasonography to measure blood flow, we hope that a comprehensive, noninvasive assessment of human fetal cardiovascular physiology in utero and later fetal cardiovascular pathophysiology may be developed.

As to Dr. Bird's question on the identification of congenital heart disease by the techniques that we have been using, we have not yet recognized any type of cardiovascular defects in those fetuses that were studied in detail for cardiovascular structure. However, this is not to say that such recognition of cardiac anomalies may not be made in the future.

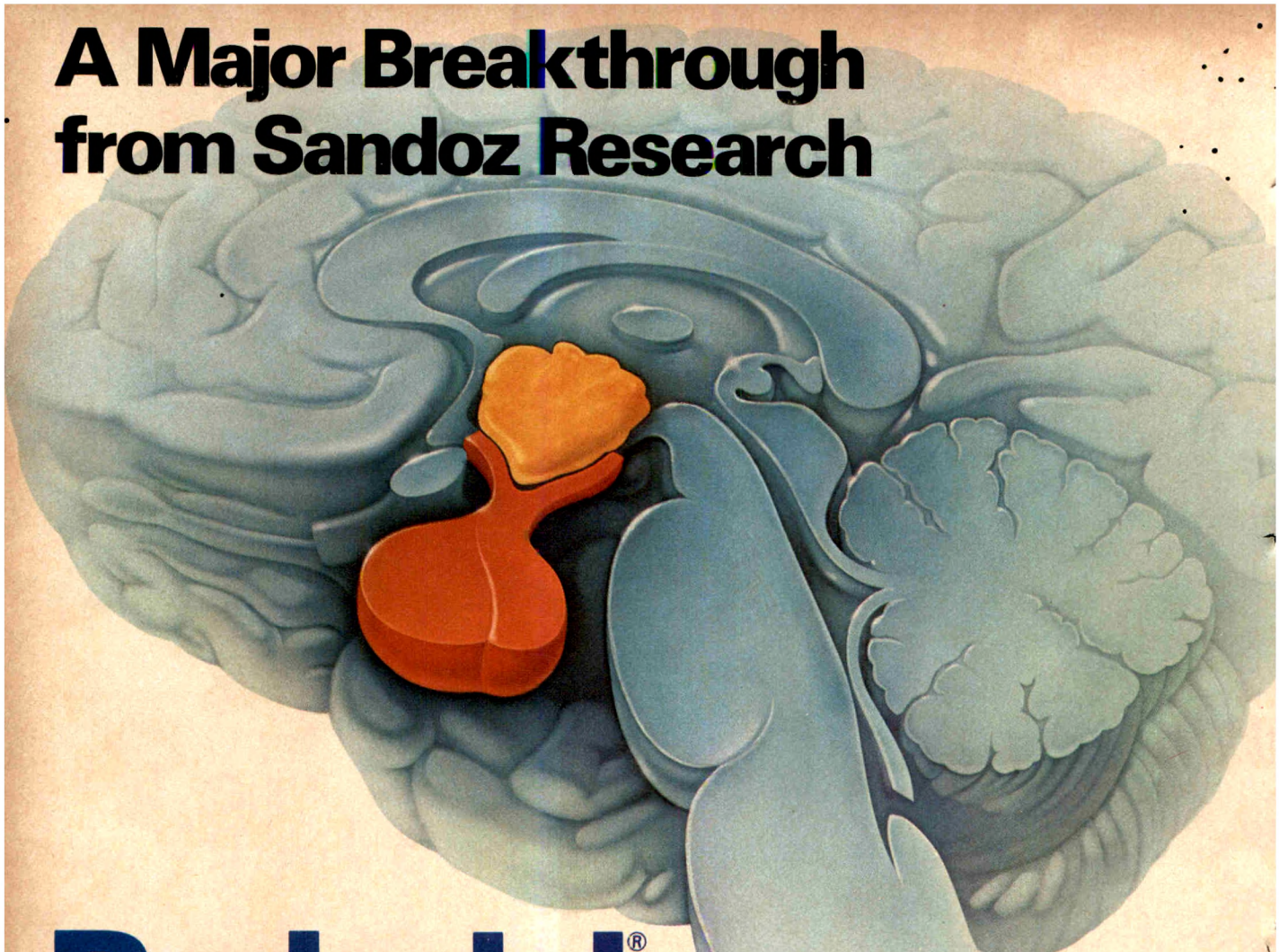
We have found that over the past 4 years of studying fetal cardiovascular structure in utero, it has taken patience, perseverence, imagination, and a little serendipity.

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  Reinitiation of menses (or pregnancy without first having menses†) was reported by 80% of 187 patients after an average treatment time of 5.7 weeks.

- **CLINICAL IMPROVEMENT IN GALACTORRHEA**
  76% of 187 patients experienced clinically significant—75% or greater—reduction in galactorrhea, and 58% experienced complete cessation of milk secretion. The treatment time required for 75% reduction was 6.4 weeks, and that for complete cessation was 12.7 weeks.

- **OVERALL CLINICAL EFFECTIVENESS**
  63% of 187 patients experienced reinitiation of menses and at least 75% reduction in galactorrhea; 47% had both reinitiation of menses and complete cessation of milk secretion.

- **CORRELATION OF CLINICAL RESPONSE WITH REDUCTION IN PROLACTIN LEVELS**
  Improvement markedly correlated with reduction in serum prolactin levels. Maximum reduction of prolactin levels was achieved within the first four weeks of therapy, and reduced levels were maintained throughout therapy.

***in the absence of demonstrable pituitary tumor. Not indicated in patients with normal prolactin levels. Safe use in pregnancy not demonstrated. Thus, not indicated in the management of infertility.**
†Parlodel (bromocriptine mesylate) is not indicated in the management of infertility.



Stylized rendition of the hypothalamus and the pituitary

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of pregnancies reported is an insufficient sample in which to detect any given birth defect; extrapolation of these data to a greater patient population would be statistically invalid.
Precautions: Since treatment may result in restoration of fertility, patients should be required to use contraceptive measures, other than the oral contraceptives, during treatment; however, since patients often ignore this recommendation and since pregnancy may occur prior to reinitiation of menses, as an additional precaution, a pregnancy test is recommended at least every four weeks during the amenorrheic period and, once menses are reinitiated, every time a patient misses a menstrual period. Parlodel® (bromocriptine mesylate) therapy has been demonstrated to be effective in the short-term management of amenorrhea/galactorrhea only. Data are not available on the safety or effectiveness of its use in long-term continuous dosage, or in patients given repeated courses of treatment following recurrence of amenorrhea/galactorrhea after initial treatment. Recurrence rates are reportedly very high, ranging from 70% to 80% in domestic and foreign studies.
Adverse Reactions: The incidence of adverse effects is quite high (68%) but these are generally mild to moderate in degree. Therapy was discontinued in approximately 6% of patients because of adverse effects. These in decreasing order of frequency are nausea 51%, headache 18%, dizziness 16%, fatigue 8%, abdominal cramps 7%, lightheadedness 6%, vomiting 5%, nasal congestion 5%, constipation 3% and diarrhea 3%. A slight hypotensive effect may accompany Parlodel® (bromocriptine mesylate) treatment. The occurrence of adverse reactions may be lessened by temporarily reducing dosage to one-half tablet two to three times daily.
Dosage and Administration: The therapeutic dosage is one 2.5-mg tablet, two or three times daily, with meals. Duration of treatment should not exceed six months. It is recommended that treatment commence with one tablet daily, increasing to a therapeutic dosage within the first week, to reduce the possibility of adverse reactions.
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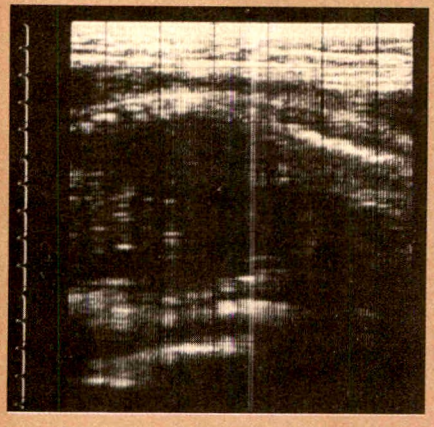
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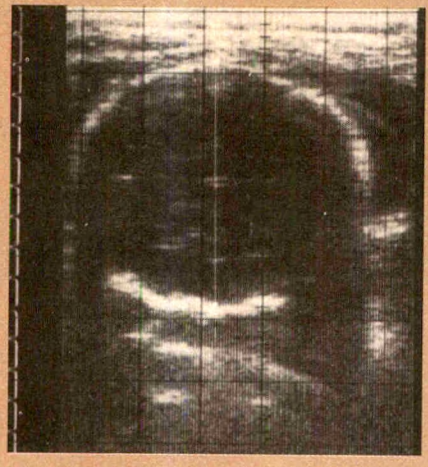
An M-Mode Cursor, exclusive with Ekolife, can be positioned through any section of the scan to record M-Mode tracings of fetal breathing and limb activity. The tracings can then be recorded on an optional strip chart recorder.



Display in 2:1 shows the trunk with the M-Mode cursor running through the heart.

The Electronic Calipers with Digital Readout permit fast, accurate determinations of biparietal diameters or crown-rump measurements right on the display.





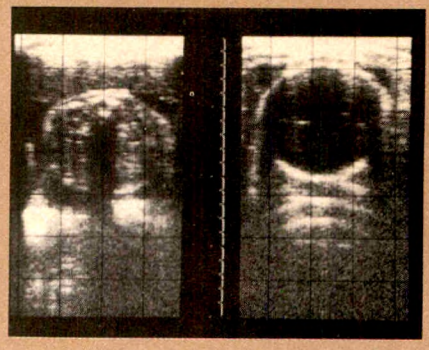
Biparietal diameter of fetal head using Electronic Calipers measurement is 8.0 cm which is approx. 33 weeks gestation.

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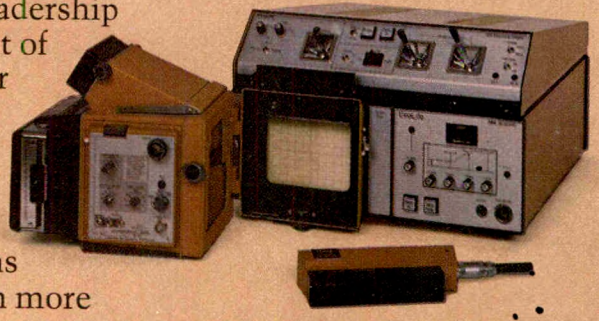
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Ten-year review of hysterectomies: Trends, indications, and risks

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This report concerns the indications, morbidity, and death associated with 6,435 consecutive abdominal and vaginal hysterectomies at Hutzel Hospital during a 10 year period. There was an extraordinary number of high-risk patients included in this group. Morbidity and postoperative bleeding were more common following vaginal rather than abdominal hysterectomy. These complications were also more common when the operation was performed during the proliferative phase of the menstrual cycle. There were 17 deaths. Thromboembolic complications were the major cause of death. Selective use of prophylactic antibiotics and low-dose heparin and reduction in the number of blood transfusions by preoperative endocrine and hematinic therapy may reduce the postoperative morbidity and mortality rates. Probably few operations will ever contribute as much to improving the quality of life of women as do indicated hysterectomies. However, the added risks do not seem to justify utilizing this operation for the sole purpose of sterilization in preference to simpler and safer procedures. (AM. J. OBSTET. GYNECOL. 134:431, 1979.)

AS THE FREQUENCY of hysterectomy has increased, the indications, risks and costs of the operation have become increasingly controversial. This analysis of over 6,000 hysterectomies was undertaken in an effort to clarify the various controversial points most frequently raised.

Study groups and methods of analysis

From 1965 to 1974, 6,435 hysterectomies were performed at Hutzel Hospital, which is the principal hospital affiliated with the Department of Gynecology and Obstetrics at Wayne State University. Of these, 90% were in private patients and one third of these had vaginal hysterectomies (Table I).

Age, parity, race, duration of hospitalization, indications, pathologic findings, morbidity, and deaths were recorded. Fewer than 1% were under 20 years of age (Table II). More than 70% were between 30 and 50 years of age. Fourteen percent were nulliparous, 74% had one to five children, and the remainder more than 5, with a maximum parity of 13 (Table III). Forty-seven percent were black and 53% were white. Duration of hospitalization ranged from 4 to 32 days, with an average of 10.5 for abdominal and 11.5 for vaginal hysterectomies.

There were 4,228 abdominal hysterectomies (67%) and 2,111 were performed vaginally. There was no significant racial difference in the number of abdominal operations. However, 1,304 (62%) vaginal hysterectomies were performed in white women, a possible reflection of the lesser incidence of uterine prolapse in black women with a greater incidence of leiomyomas.

Indications for hysterectomy

Indications for both abdominal and vaginal hysterectomies are recorded in Table IV. Uterine fibroids, adenomyosis, and endometriosis alone or in various combinations served as the indications for surgery in 4,977 (77%). Malignant disease was the indication in 626 (9%).

There has been a gradual increase in the number of hysterectomies done for leiomyoma in women of all races. This coincides with the period of increasing use of oral contraceptives but a cause-and-effect relationship has not been established. No relationship could be identified between the major blood groups and the incidence of hysterectomy for uterine fibroids.

There has been a progressive increase in the number

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Table I. Hysterectomies, 1965 to 1974

	No.	*%*
Vaginal hysterectomies	2,111	33
Abdominal hysterectomies	4,228	66
Cesarean section hysterectomies	56	1
Radical hysterectomies	40	
Total hysterectomies	6,435	100
Private patients	5,789	90
Clinic patients	646	10

Table II. Hysterectomy and age

Age	*No.*	*%*
<20	14	1
21-30	609	10
31-40	2,217	36
41-50	2,271	37
51-60	666	11
61-70	236	4
>70	113	2

Table III. Parity

	Para		
Year	*0*	*1-5*	*5*
1065	89	459	63
1966	93	404	42
1967	79	358	54
1968	62	374	54
1969	92	399	58
1970	93	433	93
1971	96	546	95
1972	92	538	79
1973	75	569	89
1974	95	654	90
Total	866	4,734	717
Percent	14	74	12

of diagnoses of carcinoma of the cervix in situ throughout the 10 year period of study. Of the 431 hysterectomies for Stage 0 carcinoma of the cervix, 273 (63%) had residual carcinoma in the hysterectomy specimen. However, these data may be spurious since they also included a group of patients who had frozen section diagnoses followed immediately by hysterectomy.

There were 39 with radical hysterectomies. Of these, 33 had invasive cancer of the cervix, five had cancer of the endometrium and regional metastases, and one had cancer of the vagina.

There were 54 who had cesarean section hysterectomies. Only two of the 24 who received prophylactic antibiotics developed evidence of infection. However, 26 (48%) received 1 to 13 units of blood transfusions.

Major complications of hysterectomy are recorded in Table V. Morbidity based on the criterion of a temperature elevation of 100.4° F on two or more occasions 6 hours apart after the first 24 hours occurred in 19%. Twelve percent received blood transfusions during or following surgery and 1.4% had significant postoperative bleeding. Fewer than 1% had any injury to the bladder, ureters, or bowel and fewer than 1% in each category developed intestinal obstruction, thrombophlebitis, and pulmonary embolism. Among those who had radical hysterectomies, 32 received 2 to 16 units of blood. Fourteen developed urinary tract infections, four had pelvic abcess, two had bladder dysfunction and wound infection, and one had a vesicovaginal fistula.

Deaths

There were 17 postoperative deaths (Table VI). Five of these patients died of pulmonary embolism, two of subarachnoid hemorrhage, and one of ruptured cerebral aneurism. There were six who died of infection, including peritonitis (three), overwhelming septicemia (two), and pneumonitis (one). Two died of widespread metastases from ovarian and sigmoid carcinomas. Only one patient died of hemorrhage. There were five who died following vaginal hysterectomy performed because of pelvic relaxation. A comparison of morbidity and death rates in this study with those in other reported series is recorded in Table VII. Ten of the 17 deaths reported here were clearly not preventable. There may have been preventable factors in the remainder, but this is debatable because of the high-risk factors involved.

Comment

During the past three decades indications for hysterectomy have been extended, with an increase in the frequency of the operation for relief of symptoms,[27] sterilization,[2] in addition to organic disease and pelvic relaxation. Despite improvements in surgical technique, anesthesia, and supportive therapy, the mortality rate associated with the operation is still significant. The added risks indicate that hysterectomy as an alternative to tubal sterilization operations is unacceptable.

Thromboembolism is still an enigma that caused almost one third of the deaths reported here. Belding[3] reported an incidence of thromboembolic disease of 1.6% in postoperative patients compared with 0.6% in this report. Low-dose prophylactic heparin offers some hope of reducing the number of deaths from this cause. Kakkar, Corrigan, and Fossard[13] administered low-dose heparin (5,000 U) just prior to and at 8 to 12 hour intervals following the operation, with a substantial reduction in the incidence of thromboembolic disease.

Table IV. Indications for hysterectomy

Indications	Abdominal		Vaginal		Black	White	Total
	No.	%	No.	%			
1. Uterine leiomyoma	2,941	76	948	24	2,683	1,206	3,889
2. Adenomyosis	559	72	216	28	346	429	775
Leiomyoma and adenomyosis	325	74	116	26	231	210	441
3. Endometriosis	301	96	12	4	94	219	313
Adenomyosis and endometriosis	55	95	3	5	17	41	58
4. Carcinoma of the endometrium	151	97	5	3	30	126	156
5. Carcinoma of the cervix, Stage 0	270	63	101	37	275	156	431
6. Invasive carcinoma of the cervix (radical hysterectomy)	39	100	0	0	14	25	39
7. Pelvic inflammatory disease	86	2.03	0	0	44	42	86
8. Uterine bleeding	326	7.7	64	3	65	325	390
9. Uterine prolapse	0	0	223	10.5	124	99	223

Table V. Complications of hysterectomy

Complications	Abdominal		Vaginal		Total	
	No.	%	No.	%	No.	%
1. Morbidity	673	16	562	26	1,235	19
Wound infections	91	0.14	216	10.2	307	4.7
2. Postoperative bleeding	36	0.9	56	2.6	92	1.4
3. Transfusion	633	15	151	7	784	12
4. Bladder injury	18	0.4	4	0.18	22	0.34
5. Ureteral injury	5	0.11	2	0.1	7	0.11
Left ureter (5)	4		1			
Right ureter (1)	1		0			
Both (1)	0		1			
6. Bowel injuries	9	0.2	0		9	0.14
Small bowel (2)						
Sigmoid 3—(2 colostomies)						
Transverse colon (2)						
Cecum (1)						
Rectum (1)						
7. Intestinal obstruction	30	0.70	21	0.99	51	0.79
8. Thrombophlebitis	16	0.37	6	0.28	22	0.34
9. Pulmonary embolism	15	0.34	2	0.1	17	0.26

Table VI. Death following hysterectomy, 1965 to 1974

Pt.	Age	Diagnosis	Procedure	Cause of death
B. G.	33	Fibroid	TAH LtSO	Pulmonary embolism
A. H.	50	Endometriosis	TAH peri. biopsy	Pulmonary embolism, carcinoma of pancreas
B. J.	52	Endometrial carcinoma	TAH BSO	Bowel obstruction, septicemia
D. G.	44	Fibroid	TAH RtSO	Subarachnoid hemorrhage
K. Z.	36	Septic abortion	TAH	Septicemia
L. M.	50	Carcinoma in situ	TAH BSO	Hemoperitoneum, subarachnoid hemorrhage
S. E.	71	Pelvic relaxation	Vag. hyst.	Inoperable carcinoma of ovary, septicemia
B. L.	55	Pelvic relaxation	Vag. hyst.	Rupture of cerebral aneurism
G. V.	69	Pelvic relaxation	Vag. hyst.	Peritonitis, atelectasis
L. B.	73	Carcinoma of endometrium	TAH BSO	Pneumonitis
J. D.	29	Pelvic relaxation	Vag. hyst.	Peritonitis
S. F.	36	Fibroid	TAH	Shock, pulmonary edema
B. I.	54	Fibroid and valvulus	TAH RtSO	Peritonitis
W. M.	48	Pelvic relaxation	Vag. hyst.	Pulmonary embolism
M. A.	60	Fibroid	TAH BSO	Adenocarcinoma of sigmoid, metastasis to ovaries and kidneys
B. M.	61	Carcinoma of cervix	Total pelvic exenteration	Pulmonary embolism
P. B.	30	Prolapse of cord	Cesarean section, hysterectomy	Pulmonary embolism

Table VII. A comparison of morbidity and mortality rates among different series of hysterectomies

Ref. No.	No. of patients	Febrile morbidity (%)		Mortality rate (%)
		Vaginal	Abdominal	
5	235	16	11	0.85
26	600	55	36	0.67
11	2,421	0	20	0.04
20	843	35.8	0	0.1
Present study	6,435	26	16	0.3

Utilization of prophylactic antibiotics, especially with vaginal hysterectomy, has become less controversial.[1, 4, 8, 12, 15, 17] Short-term utilization of antibiotics from 1 to 5 days after surgery has yielded favorable results.[1, 12, 15, 17] Such courses of therapy generally are initiated just prior to surgery. Elimination of all evidence of infection preoperatively obviously would reduce the risk of morbidity.

Attempts have been made to correlate febrile morbidity following surgery to the phase of the menstrual cycle. Neary and associates[16] found a greater proportion of positive vaginal cultures during the proliferative as compared with the secretory phase of the cycle. Galask, Larsen, and Ohm,[7] on the basis of animal experiments, suggested that estrogen promotes and progesterone decreases colonization of the genital tract. Goosenberg, Emich, and Schwarz[9] found a 25% morbidity rate after hysterectomy in postmenopausal women as compared with a 58% rate in the follicular phase and 53% in the luteal phase of the menstrual cycle of premenopausal women. Of the 6,435 hysterectomy patients in this report, 1,235 (19%) had febrile morbidity with 531 (43%) operated on during the proliferative phase and 419 (34%) during the secretory phase.

Blood transfusion remains an even greater risk factor than anesthesia.[6, 10, 14, 18, 19, 22–24] Preoperative suppression of bleeding with progestogens along with administration of iron to patients with anemia secondary to uterine bleeding has considerably diminished the need for transfusion.[21] One of the authors during the period of this study performed 64 vaginal and 134 abdominal hysterectomies without a single transfusion. The reason for the higher transfusion incidence with abdominal hysterectomy in this report was attributed to the number with uterine fibroids and secondary anemia. Postoperative bleeding was higher in vaginal hysterectomy (2.6%) than in abdominal procedures (0.9%).

Injuries to the intestinal and urinary tracts seemed to be related to the extent of surgery, indications, and anatomic distortion due to the extent of disease. When one can palpate the ureters, it is easy to avoid them. However, in the presence of extensive disease, especially endometriosis, identification of the ureter may be difficult. Preoperative intravenous pyelography is important, especially in those cases where a difficult surgical dissection is anticipated.[25]

Probably there are few operations today that contribute more to improving the quality of life of women than an indicated hysterectomy. However, the associated morbidity and mortality rates warrant critical consideration of the indications and contraindications to surgery.

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Discussion

DR. FREDERICK J. HOFMEISTER, Wauwatosa, Wisconsin. My discussion will be given as a comparative review of my experiences. I am interested in a similar project, "a study of hysterectomies performed at Lutheran Hospital of Milwaukee during a 12 year period extending from January 1, 1966, through 1977". This is being done to determine if, in fact, the unnecessary hysterectomy does dominate the surgical scene. In making this comparison, one must keep in mind that there are differences of preferred techniques, patient population, and the fact that surgery may be done by the resident or the certified gynecologist.

During the period being studied 124,517 patients were discharged. Of these, 64,354 (51.6%) were surgical patients. Do hysterectomies dominate the scene? A total of 3,484 vaginal and abdominal hysterectomies were performed; only 5.4% of surgical procedures were, therefore, hysterectomies. This is 2.79% of all patients treated during this 12 year period of time. Abdominal hysterectomies accounted for 37.5% and vaginal hysterectomies 62.5%. Pathology, indications, personal interests, and expertise may account for this figure varying from the incidence of vaginal hysterectomies (33%) and abdominal hysterectomies (66%) reported by Drs. Amirikia and Evans. All patients at our institution were of the private category. The cesarean hysterectomy incidence in abdominal hysterectomies is very comparable at both institutions—Lutheran Hospital 1.98% and Hutzel–Wayne State 1.3%.

Ages are comparable: 0.3% of patients were under 20 years of age and 68% between 31 and 50 at Lutheran Hospital; 1% were under 20 and 69.7% between 31 and 50 at Hutzel.

Hospitalization at Lutheran Hospital averaged 8 days for vaginal hysterectomies, 9.4 days for abdominal hysterectomies, and increased to 11 days when reconstructive procedures were associated with the hysterectomy.

Of the 3,484 hysterectomies performed, 2,328 (66.8%) had uterine pathology categorized as either leiomyoma or adenomyoma. This is approximately 10% less than the 77% reported by Drs. Amirikia and Evans; of the 2,176 with tumors, 62% were performed vaginally.

Carcinoma of the uterus, endometrial, or in situ carcinoma of the cervix accounted for 225 (6.45%) of cases in our series.

Another 265 hysterectomies were listed as having no uterine pathology; these included salpingitis, ovarian carcinoma, endometriosis, pelvic abscesses, tuboovarian abscesses, and peritonitis with massive pelvic adhesions. These total 7.6% of all hysterectomies or 20.2% of abdominal hysterectomies.

It must be noted that the preceding cases tabulated as having no uterine pathology along with another 360 (10.3%) of hysterectomies which were performed for uterine prolapse, extensive pelvic relaxation, cesarean hysterectomy, and placenta accreta were also tabulated as having no uterine pathology. Would surgery under these conditions be regarded as unnecessary and unjustified by a person reviewing the chart, who is inexperienced and lacks clinical judgment?

Certainly when the final diagnosis is listed as chronic cervicitis, endocervical polyp, nabothian cyst, enlarged uterus, or "no reason", as in 425 (12.1%), I could agree that no uterine pathology was present. However, we must look deeper. There are no hysterectomies in our series listed as done for sterilization. Were physicians fabricating pathology to justify hysterectomy? Could this be the reason? I, personally, would advise my patient requesting a tubal interruption who had a history of menometrorrhagia or when palpable uterine fibroids are detected to have a hysterectomy. This is my concept of good therapy, but I would make this very clear on the records.

Complications causing postoperative morbidity existed in 65 vaginal hysterectomies and 38 abdominal hysterectomies, a total of 103 cases (2.9%). Included in these are excessive blood loss. In 26 (0.74%) of hysterectomies, hematoma formation or excessive blood loss was mentioned. Only six of these required transfusion (0.17%). These data date back to the time before the intelligent use of prophylactic antibiotic coverage was started. Presently I use antibiotics when either one or both tubes and ovaries are retained in both vaginal and abdominal cases. I also use antibiotics when the patient has had or has pelvic inflammatory disease, but not routinely in all hysterectomies.

How many deaths were associated with our series? There were three (0.086%): (1) fifth day postoperative—ventricular fibrillation and pulmonary edema, (2) fifth day postoperative—coronary occlusion, and (3) cardiac arrest in the recovery room.

I believe the authors have indicated the justification of a procedure which is not a rip off of the public and that they, as we, believe hysterectomy to be a valuable and necessary health-restoring surgical procedure.

DR. BRUCE C. RICHARDS, Lakewood, Colorado. Dr. Amirikia stated that as the frequency of hysterectomy has increased, the operation has become increasingly controversial, and I agree. Did you know that a woman's lifetime chance of having a hysterectomy in 1965 was 62%? Did you know that there were 751,000 hysterectomies done in 1976?[1]

Taking the PAS figures in 1972, the mortality rate for hysterectomy is 16.4 per 10,000. These figures, as you know, are taken from a broad range across the country. This is one half the mortality rate of appendectomy and one eighth that of cholecystectomy.[2] The mortality rate at Wayne State University–Hutzel Hospital for hysterectomies with 90% private patients is 26.4 per 10,000.

In the time available, I checked a sample of 1,065

consecutive hysterectomies done at a small hospital in Wheatridge, Colorado. There were no deaths. Without being able to prove it, I think there have been only two deaths in over 10,000 cases at this hospital.

The vast majority of these patients were white. The average hospital stay was 7.3 days abdominally and 6.3 vaginally vs. 10.5 and 11.5.

There were 60% of these hysterectomies performed vaginally compared with 33% in Detroit. Of those vaginal hysterectomies, 42% had a uterus weighing over 150 grams.

On a smaller sample (701) based on the same febrile morbidity definition, there were 26% with abdominal and 3% with vaginal hysterectomies vs. 16% and 26%. There *were* other complications that did not show as febrile. Notice, please, the great disparity in the vaginal figures and notice that morbidity and length of stay for vaginal hysterectomies are now less than abdominal.

I only wish to make one point. It certainly is not that the staff of that small hospital is any better than that of Hutzel Hospital in Detroit. In the first place, with prophylactic antibiotics, these recent statistics should be better than those from 10 years earlier. There were no radical hysterectomies. We do not have a residency staff. Our patients, I would have to think, would have over-all better health and probably less technically complicated surgery.

Although the authors promised to "clarify the various controversial points" regarding hysterectomy, they failed to do so. I also maintain that their figures, while impressive and coming from a large number of hysterectomies and a great Department of Gynecology, do not reflect the over-all statistics of the ordinary hospitals, where the vast majority of gynecologic work is done and done excellently. I would, therefore, suggest that their figures should not be accepted as standard.

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DR. EVANS (Closing). I quite agree that there is probably no operative procedure carried out today that contributes more to improving the quality of life for women than does a hysterectomy, but it is important that we look very critically at the indications and the morbidity and mortality rates.

I think Dr. Richards should re-read the first paragraph. There was no promise to resolve the controversy; this study was undertaken in an attempt to try to resolve some of these issues. I now think that many of them can only be resolved in terms of prospective studies.

As we look into the future, I believe there will be a lot of differences in the categories of patients subjected to hysterectomy. For example, the large number who were operated on for bleeding without demonstrated pathologic change in the specimen is really no longer acceptable. Very, very few patients should ever have a hysterectomy just because of bleeding. That is an endocrine disease largely, and in most instances it can be treated medically and not surgically.

With regard to sterilization as an indication for hysterectomy, I agree with Dr. Hofmeister. I think, when there is a composite picture, where sterilization is a major consideration, but there are other concurrent indications, that perhaps there is a combined indication for hysterectomy. I support completely what Dr. Amirikia has said. There is no excuse for substituting a more major and riskier procedure for a simple, one-day in-and-out procedure to accomplish sterilization unless there are other indications as well.

Also, I think it would be pretty easy for many of the excellent gynecologic surgeons in this room to report a series of a thousand consecutive hysterectomies without appreciable morbidity or mortality rates, but there have to be institutions where this is not true. We have many, many high risk patients in our hospitals, and they are both in the private category as well as in the staff category. However, it is interesting to note that for 4 consecutive years the obstetric and perinatal mortality rates for the high-risk staff patients have been lower than for the private patients in the same institution. There have to be places for referral of high-risk patients. I am pretty sure if I were in private practice that a number of the patients in the mortality group would have ended up being referred to such a center as the Hutzel Hospital.

I am impressed about the low mortality rate in the patients with endometrial cancer. One died of bowel obstruction, another of sepsis. When you think of the tremendous number of high-risk patients subjected to operation for endometrial cancer, some weighing 300 and 400 pounds, I think such a low mortality rate is impressive.

I believe the final vote is not with respect to prophylactic antibiotics. I use prophylactic antibiotics as Dr. Hofmeister does, on a very selective basis in patients at high risk. I think the patient population that is being analyzed in terms of morbidity and death from hysterectomy is of critical importance. We all should look just as critically at posthysterectomy mortality cases as we do at maternal mortality cases to identify preventable factors to guide us in the future. Certainly we need to do an analysis of deaths in these patients.

Also, we should see fewer deaths in the future with the progressive decrease in the number of transfusions which are required. One can frequently avoid transfusions in patients even if they are severely anemic by giving them prophylactic progestogens and iron preoperatively. This can greatly reduce the risk of anemia, which can be greater than the risk of anesthesia.

I agree with Dr. Richards regarding the duration of hospitalization. I think it should be progressively shorter and shorter. This will be reflected by the nature

of the patient population, and whether they are at risk medically and or have been in the hospital for some days on the medical service before being subjected to operation. Over the 10 year period of Dr. Amirikia's investigation, there has been a progressive decline in the duration of hospitalization. Of course, there are variables, as exemplified by the patient who has a vaginal hysterectomy, as to whether there is a concurrent anterior and posterior repair done. The combined operation may be the reason for prolongation of hospitalization and not the vaginal hysterectomy alone.

One can do anything with statistical evaluations. I believe we should look very critically at each individual death. I hope, with the proper use of selective prophylactic antibiotics and low-dose anticoagulants, we can greatly reduce the mortality rate in the future.

Unsuspected subclinical pregnancies in patients with luteal phase defects

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Patients with different types of luteal phase defects were studied with the use of the radioimmunoassay for the beta subunit of human chorionic gonadotropin (hCG) to determine if unsuspected subclinical pregnancies were more common in a particular type of defect. A type I luteal phase defect is always characterized by a chronologic lag in endometrial development when repeatedly studied with timed endometrial biopsies. A type II luteal phase defect is always characterized by an in phase endometrium when repeatedly studied by timed endometrial biopsies but always has less than a 14 day luteal span. All blood samples were drawn at least 7 days after ovulation/conception. In 22 cycles in which patients had a type I luteal phase defect, no subclinical pregnancies were detected. In 18 cycles in which a type II luteal phase defect was present, 12 instances of unsuspected subclinical pregnancy were detected and all ended in spontaneous abortion. This study shows that unsuspected subclinical pregnancies ending in abortion do occur and are quite commonly associated with the type II luteal phase defect. (AM. J. OBSTET. GYNECOL. 134:438, 1979.)

A CLASSIFICATION of luteal phase defects and possible etiologies was recently presented.[1] To review briefly, a type I luteal phase defect is characterized by a lag in the chronologic development of the endometrium with or without a short luteal span. The etiology of this defect is probably central. A type II luteal phase defect is characterized by in phase endometrial development but has a short luteal span. The etiology of this defect may be peripheral but is probably central, specifically a probable decrease in the length of time that luteinizing hormone (LH) is secreted from the pituitary.

Following this model one would expect to see few unsuspected subclinical pregnancies with a type I luteal phase defect because the endometrium is not adequately developed for proper implantation and placentation. Conversly, patients with a type II luteal phase defect would be expected to have frequent unsuspected subclinical pregnancies since the endometrium is developed in phase and will allow implantation and early placentation but the luteal phase duration is too short to allow the rescue phenomenon to occur.

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Braunstein and associates[2] stated that the factors that predispose to early subclinical abortions are unknown. This study was conducted to determine if the detection of unsuspected subclinical pregnancies using radioimmunoassay of the beta subunit of human chorionic gonadotropin (hCG) would conform to the model presented and thereby elucidate at least one predisposing factor.[3]

Material and methods

Radioimmunoassay. The hCG beta subunit radioimmunoassay was used to measure hCG in serum samples.[3] There is no cross-reaction with human pituitary LH in physiologic concentrations.

Samples. Blood was obtained by venipuncture and the serum was rapidly separated from the clot and stored between −4° and −20° C until assayed. All samples were drawn at least 7 days after ovulation/conception. Any specimen with over 20 IU/ml was considered compatible with pregnancy.

Patients. Patients with various types of ovulatory defects and luteal phase defects were studied under a variety of treatment programs, utilizing the hCG beta subunit as an indicator of unsuspected subclinical pregnancy. These patients were all seen in my private infertility practice. All other causes of infertility had previously been investigated and either treated or ruled out.

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Table I. Comprehensive chronologic table showing 17 patients with diagnoses, treatment regimens, results of the hCG beta subunit radioimmunoassay, time of the onset of menses, results of a repeated biopsy, and outcome of clinical pregnancy

Patient	*Initial and subsequent diagnoses*	*Treatment*	*Radioimmuncassay of β-HCG (IU/ml/luteal day)*	*Results*
J. W.	Type I defect		<3.2 ov. +11	Menses ov. +13
			<3.2 ov. +12	Menses ov. +14
		Clomid, 100 × 5	28.5 ov. +11	Menses ov. +12
				Type II defect
	Type II defect	Clomid, 100 × 5 hCG after ov.		Pregnant-delivered at 40 wk.
C. S.	Type II defect		21.2 ov. +9	Menses ov. +11
S. S.	Type II defect		69.0 ov. +14	Menses ov. +18
			<3.2 ov. +11	Menses ov. +12
		hCG after ov.		Pregnant—delivered at 38 wk.
R. S.	Type II defect		40.6 ov. +13	Menses ov. +16
			<3.2 ov. +11	Menses ov. +12
		hCG after ov.		Pregnant—delivered at 38 wk.
N. R.	Anovulation	Clomid, 100 × 5		Ovulation
				Type II defect
	Type II defect	Clomid, 100 × 5	<3.2 ov. +10	Menses ov. +12
		Clomid, 100 × 5	36.0 ov. +10	Menses ov. +14
		Clomid, 100 × 5 hCG after ov.		Pregnant—delivered at 40 wk.
C. P.	Type II defect			Menses ov. +10
			94.5 ov. +25	Menses ov. +26
			>125.0 ov. × 27	Delalutin, pregnant—delivered at 41 wk.
S. M.	Type I defect		<3.2 ov. +10	Menses ov. +14
			<3.2 ov. +10	Menses ov. +13
		Clomid, 100 × 5	<3.2 ov. +10	Menses ov. +14
				Biopsy corrected
		Clomid, 100 × 5	<3.2 ov. +10	Menses ov. +14
		Clomid, 100 × 5	29.0 ov. +11	Pregnant—delivered at 40 wk.
M. M.	Type I defect		<3.2 ov. +10	Menses ov. +14
		Clomid, 50 × 5	<3.2 ov. +11	Menses ov. +14
				Type I defect
		Clomid, 100 × 5	<3.2 ov. +12	Menses ov. +13
				Type I defect
		Clomid, 150 × 5	<3.2 ov. +11	Menses ov. +14
				Biopsy corrected
	Corrected biopsy	Clomid, 150 × 5	21.0 ov. +12	Pregnant—delivered at 41 wk.
			>200.0 ov. +33	
L. M.	Anovulatory	Clomid, 50 × 50		Anovulatory
		Clomid, 100 × 5		Menses ov. +10
	Ovulatory	Clomid, 100 × 5	<3.2 ov. +10	Menses ov. +11
				Type I defect
	Type I defect	Clomid, 150 × 5	22.1 ov. +11	Menses ov. +11
				Type II defect
	Type II defect	Clomid, 150 × 5 hCG after ov.		Menses ov. +14
	Corrected defect	Clomid, 150 × 5 hCG after ov.		Pregnant—delivered at 37 wk.
J. K.	Anovulatory	Clomid, 50 × 5		Menses ov. +13
	Ovulatory	Clomid, 50 × 5	<3.2 ov. +10	Menses ov. +14
				Type I defect
	Type I defect	Clomid, 100 × 5	<3.2 ov. +12	Menses ov. +13
				Type I defect
		Clomid, 150 × 5	<3.2 ov. +12	Menses ov. +13
				Type I defect
		Clomid, 150 × 5	21.5 ov. +10	Menses ov. +12
				Type II defect
	Type II defect	Clomid, 150 × 5 hCG after ov.		Menses ov. +14
	Corrected defect	Clomid, 150 × 5 hCG after ov.		Pregnant—delivered at 39 wk.
P. L.	Type I defect		<3.2 ov. +10	Menses ov. +13
		Clomid, 50 × 5	<3.2 ov. +10	Menses ov. +14
				Biopsy corrected

continued

Table I—Cont'd

Patient	*Initial and subsequent diagnoses*	*Treatment*	*Radioimmunoassay of β-HCG (IU/ml/luteal day)*	*Results*
(P. L.—cont'd.)				
	Corrected biopsy	Clomid, 50 × 5	26.0 ov. +11 >200 ov. +28	Pregnant—delivered at 37 wk.
J. J.	Anovulatory	Clomid, 50 × 5	<3.2 ov. +9	Menses ov. +14 Biopsy corrected
	Corrected biopsy	Clomid, 50 × 5	160.0 ov. +30	Pregnant—21 wk.
S. H.	Type II defect		<3.2 ov. +10 24.5 ov. +11 64.0 ov. +18	Menses ov. +11 Menses ov. +13 Menses ov. +20
		hCG after ov.		Pregnant—24 wk.
C. F.	Type I defect	Clomid, 100 × 5	43.1 ov. +14	Menses ov. +15 Corrected biopsy
	Corrected biopsy	Clomid, 100 × 5	36.0 ov. +14 67.0 ov. +21	Pregnant—delivered at 39 wk.
P. D.	Type II defect		22.0 ov. +12 <3.2 ov. +12 <3.2 ov. +12 28.0 ov. +11	Menses ov. +12 Menses ov. +12 Menses ov. +12 Menses ov. +12
		hCG after ov.		Pregnant—delivered at 42 wk.
M. B.	Type I defect		<3.2 ov. +12 <3.2 ov. +11 <3.2 ov. +11	Menses ov. +12 Menses ov. +11 Menses ov. +12
		Clomid, 100 × 5	<3.2 ov. 10	Menses ov. +12 Type I defect
		Clomid, 150 × 5	<3.2 ov. +10	Menses ov. +12 Type I defect
		Clomid, 150 × 6	<3.2 ov. +11	Menses ov. +12 Type II defect
	Type II defect	Clomid, 150 × 6 hCG after ov.		Pregnant—delivered of twins at 37 wk.
K. T.	Type I defect	Clomid, 100 × 5	<3.2 ov. +10	Menses ov. +14 Type I defect
		Clomid, 150 × 5	<3.2 ov. +9	Menses ov. +14 Type I defect
		Clomid, 150 × 6 hCG, 10,000 IU		Type I defect
		Human menopausal gonadotropin–hCG		Corrected biopsy
	Corrected biopsy	Human menopausal gonadotropin–hCG		Pregnant—delivered at 40 wk.

Results

Seventeen patients were studied in the luteal phase utilizing the hCG beta subunit radioimmunoassay to detect subclinical pregnancies. Many patients were studied in more than one treatment cycle under various treatment regimens and therefore had different treatment cycles. For example, many patients with a type I luteal phase defect will experience conversion to a type II luteal phase defect under certain treatment regimens.[1] Table I shows 22 cycles in which the patient had a type I luteal phase defect and no subclinical pregnancies were detected. In 18 cycles in which a type II luteal phase defect was present, 12 instances of unsuspected subclinical pregnancy were found and in all 12 cases an early subclinical spontaneous abortion occurred. Tables II, III, and IV further clarify this study.

Comment

This study has shown and confirmed that subclinical abortions do occur. The cause of these subclinical abortions may at times be developmental abnormalities incompatible with life or a poor nidation site such as an intrauterine septum or myoma. This study, however, has shown that the type II luteal phase defect is quite commonly associated with subclinical spontaneous abortions.

Since no pregnancies were detected in 22 cycles in which a type I luteal phase defect existed, it can be assumed that an endometrium out of phase is usually not compatible with even early implantation and placentation. When patients with a type II luteal phase defect were studied, two of three showed unsuspected subclinical pregnancies which ended in subclinical

Table II. Menstrual cycles and treatment

Cycle	Total	No. without treatment	No. with treatment
Anovulatory	4	0	4
Type I defect	20	9	11
Type II defect	19	14	5
Viable pregnancy	16	1	15
Conversion to "in phase" endometrium	10	0	10
Total	69	24	45

Table III. β-hCG valves

Cycle	Total	No. without treatment		No. with treatment	
Anovulatory	4	0	(0*)	4	(0)
Type I defect	20	9	(0)	11	(0)
Type II defect	19	14	(8)	5	(1)
Viable pregnancy	16	1		15	
Conversion to "in phase" endometrium	10	0	(0)	10	(4)

*No. with β-hCG >3.2 IU/ml.

spontaneous abortions. Since the type II luteal phase defect by definition is characterized by an in phase endometrium but a short luteal span, one would anticipate these findings. Likewise, if one could lengthen the luteal span of patients with a type II luteal phase defect to allow the rescue phenomenon to occur, one would expect a considerable increase in salvageable subclinical pregnancies.

Table IV. Cycles terminating in subclinical abortion in eight patients with type II defects and β-hCG values <3.2 IU/ml

β-hCG (IU/ml)	Outcome: Serum sample drawn (days after ovulation)	Outcome: Bleeding began (days after ovulation)
Subclinical abortion:		
21.2	9	11
22.0	12	12
24.5	11	13
28.0	11	12
40.6	13	16
Clinically evident abortion:		
69.4	14	18
64.0	18	20
94.5	25	26

I would like to thank Dr. William Wahle of the Department of Pathology, St. Vincent Hospital and Health Care Center, Indianapolis, Indiana, for his assistance in performing the radioimmunoassay for the beta subunit of hCG and for his help in compiling the data used in this study. The assistance of the Department of Medical Affairs, St. Vincent Hospital and Health Care Center, is also greatly appreciated.

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Discussion

Dr. Carolyn B. Coulam, Rochester, Minnesota. Dr. Cline's observation of the occurrence of subclinical pregnancies diagnosed by elevated β-subunit hCG in infertile patients has furnished a contribution to knowledge in this field. I am sure that he will not object to a slightly different interpretation of his data, especially since the conclusion is relatively similar.

Dr. Cline's Table I presents data on 17 patients in whom a total of 69 menstrual cycles are noted. Of the 69 cycles, four were described as anovulatory, 20 as type I luteal phase defects, 19 as type II luteal phase defects, 16 as viable pregnancy cycles, and 10 as cycles during which the endometrium converted to an "in phase" endometrial biopsy pattern. Of the 69 cycles described, there were 45 in which the patient was undergoing treatment and 24 in which no treatment was given, as summarized in Table II.

When those cycles in which a viable pregnancy was the outcome are eliminated, there were 13 instances in which a β-subunit hCG value was reported to be greater than 3.2 IU/ml, as shown in Table III.

At this point I would disagree with Dr. Cline's interpretation that a type I luteal phase defect is associated with no subclinical pregnancies because the endometrium is not adequately developed for proper implantation. The interpretation of Strott and colleagues[1] that the deficit is in the failure of adequate follicular maturation and ovulation rather than in luteinizing or "luteotrophic" hormone is a more likely explanation. Therefore, I would classify this group with the anovulatory cycles. Assuming that the remainder of the groups, including those with type II luteal phase defects as described, represent ovulatory cycles, a comparison of the pregnancy and abortion rates can be made between those receiving some form of treat-

ment and those receiving no treatment. I have placed the type II luteal phase defects in the ovulatory group because none of the cycles was described as having a luteal phase of less than 10 days.

Directing attention to only the ovulatory cycles in Table III, there are 15 cycles in which no treatment was received and 30 cycles during which various forms of treatment were undertaken. During the 30 treatment cycles, there were 20 pregnancies, for a pregnancy rate of 67%, and five abortions, for an abortion rate of 17%. These figures do not differ from expected pregnancy rates after induction of ovulation[2] or from previously reported spontaneous abortion rates.[3, 4] During the 15 nontreatment cycles, nine pregnancies occurred, for a pregnancy rate of 60%, which differs little from the pregnancy rate during the treatment cycles. However, eight of these nine pregnancies terminated in abortion, for an abortion rate of 53%—clearly higher than the expected rates previously reported. If we look closer at the eight cycles that terminated in abortion (Table IV), we can see that five of the eight could be classified as subclinical, because they occurred within the first 2 weeks of gestation. In the remaining three abortions, termination of pregnancy occurred after the second week of gestation and therefore would be clinically evident. These three clinically evident abortions represented a clinical abortion rate of 20%, which differs little from the spontaneous abortion rates previously reported, as above. This leaves a subclinical abortion rate of 33%, which is elevated over previously reported spontaneous abortion rates. However, I know of no data describing subclinical abortion rates as evidenced by elevated β-unit hCG in a normal fertile population. I am interested in knowing whether Dr. Cline has any such data to serve as a control.

Assuming that this subclinical abortion rate is elevated, an explanation for such an event can be gleaned by reviewing recent knowledge of receptor physiology. Follicular maturation and luteinization are associated with the appearance of receptors for follicle-stimulating hormone (FSH), estrogen, testosterone, LH, prolactin, and prostaglandins.[5] Once induced, normal corpus luteum function requires the continuous presence of small amounts of LH, and the decline of this function is associated with a decrease in the response of the luteal cells to gonadotropin. The inability of human corpus luteum cells to respond to LH in the late luteal phase may be associated with the loss of LH receptors. If corpus luteum dysfunction occurs because of a deficiency in LH receptors, and LH receptors are induced by FSH and augmented by estrogen, it is no difficult to envision a cause of this defect occurring before ovulation. It is not surprising, therefore, that this defect can be treated with ovulation-inducing drugs that enhance follicular maturation, as Dr. Cline's data suggest.

There is no evidence that other lutectropic hormones, such as prolactin, or luteolytic substances, such as prostaglandins, play a role in the human menstrual cycle. The one known luteotropin in man, hCG, which was present in the sera of Dr. Cline's patients in significant quantities, apparently was not sufficient to prevent subclinical pregnancy loss. This fact lends further support to a deficit in receptor activity as a cause of type II luteal phase defects, since LH and hCG receptors are probably the same.[6]

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DR. ASGHAR AFSARI, Bloomfield, Michigan. The luteal phase defect is defined as an inadequacy of corpus luteum in the production of progesterone in either amount or duration or both.[1] The deficiency of function of the corpus luteum is now generally accepted as a definite but uncommon cause of infertility in women. Clinically it is regarded as causing an undesirable environment for a successful gestation by interfering with implantation or as causing an early occult abortion.[2] The incidence of this defective function is approximately 3.5% in a population of infertile patients. Similarly, among patients with habitual abortions, this problem is identified with a much higher frequency, in about 35% of cases. The higher incidence of an inadequate luteal phase among this particular group of patients is another indication of an endocrine problem rather than an anatomic anomaly.[5] The deficiency is not due to a single etiologic factor. Several factors have been implicated,[1] namely, defects of the hypothalamic-pituitary axis, ovarian defects, metabolic defects, and specific defects in luteal cell steroidogenesis. The relative deficiency of FSH during the follicular phase, an inappropriate FSH/LH ratio, and an inadequate tonic residual LH in the secretory phase are accepted to be the major causes of this entity. Moreover, a high level of prolactin, which may inhibit the cyclic pattern of FSH and LH secretion and thereby produce a luteal phase defect, has been suggested recently.[4]

The best result of treatment has been gained with the use of progesterone suppositories, with a success rate of 48% to 50% reported by Jones[1] and Soules.

In reviewing the manuscript, the tables were somewhat confusing and difficult to interpret. According to the tables, only one of 17 patients was not found to be pregnant, but the remaining patients were all respon-

sive to the therapy. This result is even more impressive after learning about the modalities of treatment. I wonder if Dr. Cline would elaborate on the results and the treatment, and also on any particular experience with the progesterone suppository.

Regarding the use of radioimmunoassay of the beta subunit of hCG, the incubation period of the test is described as being 24 to 72 hours, and I wonder if any consideration has been given to the use of radioreceptor assay (RRA) of hCG.[5] It has been proved that the quantitative RRA of hCG requires not more than a 15 minute incubation period and is highly sensitive, detecting as low as 6 mIU/ml or 0.5 ng/ml with the earliest detection time of hCG 6 to 8 days after ovulation. This might also help in further appropriate management and follow-up of these very anxious patients.

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DR. R. RALPH MARGULIS, West Bloomfield, Michigan. The problem of luteal phase defect has been researched and widely discussed. This entity was initially brought to our attention by the presentation of Jones of the Johns Hopkins group although its validity has been doubted by many gynecologists.

I was interested in Dr. Cline's classification, based on length of luteal phase and type of endometrium. At William Beaumont Hospital in Royal Oak, we use a classification based on etiologic factors. For management purposes, this subdivides logically into two groups—those having normal prolactin levels and those with elevated prolactin levels.

Therefore, I would like to propose for clarification the following classification of deficient corpus luteum function, depending upon where the deficiency originates: (1) hypothalamic defect, (2) pituitary site, (3) ovary, and (4) partially unresponsive endometrium (theoretical, but not very likely). Those patients with this defect who demonstrate a normal serum prolactin level can usually be managed by the administration of clomiphene and/or hCG. A diminution in FSH production will in turn reduce the LH receptors of the follicular apparatus and, therefore, become a contributory factor in the eventual diminished production of progesterone. Clomiphene acts to increase FSH, thereby increasing follicular growth and, thus, producing increased estrogen and LH receptors. hCG acts as LH and leads to increased progesterone production. Management with progesterone alone will affect only the endometrium, since its influence on LH is unpredictable.

Many patients exhibiting this problem will have elevated levels of prolactin. Hyperprolactinemia will affect the hypothalamic release of gonadotropin-releasing hormone (GnRH), thus diminishing the secretion and release of FSH and LH from the pituitary. Through the mechanism discussed a moment ago, this indirectly leads to a reduction in progesterone. Cases with hyperprolactinemia may be successfully managed with bromocriptine (Parlodel) which will be effective at the hypothalamic, pituitary, and ovarian levels. Bromocriptine will: (1) increase dopamine receptors, thus increasing GnRH release, resulting in secretion and release of FSH, (2) decrease prolactin secretion by increasing the hypothalamic prolactin inhibiting factor, and (3) work directly on the ovarian follicular apparatus by blocking prolactin receptors and allowing LH receptors to function in stimulating production of progesterone. It has been proved that in the presence of increased prolactin, tissue cultures of granulosa cells do not produce progesterone. European investigators have been using bromocriptine successfully in correcting corpus luteum deficiencies.

PROFESSOR RONALD W. TAYLOR, London, England. We in our unit would agree with Dr. Cline in his conclusions. We have not used the same sort of classifications he has, but we have experience with 215 patients referred to us by other gynecologists in whom no obvious cause existed for their infertility. Prolactin levels within the upper limits of normal or above the limits of normal were found in more than 30% of these patients.

We have treated such patients both with clomiphene and with bromocriptine with 34 pregnancies resulting from clomiphene and 19 pregnancies from bromocriptine. An additional two patients became pregnant after treatment with hCG.

I very much endorse what has been said about the management of the patient with elevated prolactin values. This is important because it concerns the steroidogenesis in the corpus luteum. However, there is one additional factor which we have found in our investigations. We have been using Peridoxin (vitamin B_6) in a dose of 40 mg twice a day, providing patients do not have microadenoma of the pituitary which is responsible for the raised prolactin levels. There is something over a 60% chance that these patients will respond with a lowering of the elevated prolactin level. Unfortunately bromocriptine has many side effects. While we agree that it is very valuable, we recommend that a primary treatment in such patients be with Peridoxin because it is so innocuous and in our experience is very well worthwhile.

DR. JOHN S. GILLAM, Brekenridge, Minnesota. I

presented an almost identical paper 25 years ago, but I did not have the smart young men working with me that we have today. It has been very gratifying to hear of the clinical and laboratory correlations which have been revealed in this paper. I think that, like the work of Hertig, Rock, and Noyes, this research has contributed significantly to an improved understanding of this entity.

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DR. JOE L. SIMPSON, Chicago, Illinois. While Dr. Cline is perhaps correct in assuming that there can be some subclinical pregnancies due to a type II luteal phase defect, I think it might be appropriate at this point to recall the weight of the evidence that suggests, in humans as well as in practically all animal studies, anomalies and chromosome abnormalities incompatible with life are certainly responsible for the loss of the vast majority of subclinical pregnancies.

For example, if we recall the work of Hertig and Rock who recovered preimplantation and early implanted embryos from a series of fertile patients, four of eight preimplanted embryos, which were less than 6 days of age, were so morphologically abnormal that continuation of the pregnancy could not have been expected. Likewise, among the early implanted embryos, the figures were something like eight of 26 which were incompatible with survival.

In very early preimplanted embryos from rodent species, it can be shown that a vast majority of chromosomal abnormalities present are not compatible with continued embryonic development. For example, YO mice can be recovered at the four-cell stage and monosomies and trisomies demonstrated. I think that the findings that Dr. Cline has shown us are quite relevant, but it should be remembered that his thesis is applicable to only a specific subset of the population. Overall, I think it is wise to remember that the vast majority of early losses are likely to be of genetic rather than endocrine etiology.

DR. CLINE (Closing). Regarding the comments of Dr. Coulam, I think she and I agree. My feeling is that the endometrium in the type I luteal phase defect is not in phase because of an inadequate, immature follicle.

Since I wrote this original small paper, we have studied various treatment modalities, and I have found that the preovulatory urinary estrogen level is always less than 50 μg/24 hours prior to the LH surge in the type I luteal phase defect. Once this defect is either converted or corrected, it goes hand in hand that the urinary estrogen excretion always rises to over 70 μg/24 hours in the treatment study. I think this goes along with the concept of the inadequately mature follicle.

I personally do not have any hCG data in a normal population.

Regarding Dr. Afsari's comments about luteal phase defects being uncommon, I will take considerable issue with that because I find these defects to be extremely common, and I, too, have many referrals from doctors who have done everything they can in treatment of patients. Most of these patients have been on a regimen of clomiphene for months and months and months.

What I am trying to say is that when a patient has had long-term clomiphene administration, rebiopsy should be performed. Just because these patients "look good on paper," they ovulate, and they have a 14 day luteal phase does not mean that they cannot have an endometrium completely out of phase and a preovulatory urinary estrogen excretion of less than 50 μg/24 hours. We have adopted, in my office, a philosophy of treat and biopsy, treat and biopsy, etc., until the defect is either converted or corrected.

Some of these patients will experience correction with Clomid or Clomid, Premarin, and hCG, and then Pergonal therapy will result in correction.

I did not use the radioreceptor assay because at the time I considered it probably not sensitive enough and still consider this to be true.

Regarding the question of receptors, this is certainly interesting and almost certainly correct and probably goes along with the estrogen studies that we have available now, but the preovulatory estrogen studies we have now have not been presented or published.

Regarding Dr. Taylor's comment, I personally have not studied ovulatory patients, regarding the prolactin levels, but certainly appreciate his comments and probably will do so in the future.

Finally, concerning the genetic aspect of all of this, I, too, have found translocation carriers in patients with early subclinical abortions but have not been able successfully to treat them and did not try.

Ovarian hyperandrogenism with normal and abnormal histologic findings of the ovaries

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Thirty-one patients with clinical features of polycystic ovary syndrome (PCO) were studied to determine the correlation between biochemical and histologic findings. The biochemical features investigated were the effects of adrenocortical and ovarian suppression by dexamethasone and oral contraceptives (Ovulen) on plasma free androgens. Four patients showed a histologic picture consistent with PCO (Group A), and five had histologically normal ovaries (Group B). The remaining 22 patients had no tissue available for histologic examination (Group C). The baseline values of plasma free testosterone (FTeI) were higher and those of testosterone-binding globulin (TeBG) were lower ($p < 0.05$) in Group A than in Group B, although plasma total testosterone (T) and the free 17β-hydroxysteroid androgen index (FHSI) were similar in the two groups. During dexamethasone administration in all study groups, T and FTeI fell slightly (17.7% to 33.8%), and FHSI levels decreased moderately (36% to 46.6%); in no case did both indices of free androgen levels fall to the normal range for dexamethasone-suppressed women. However, no change was noted in TeBG in all three groups. On the other hand, Ovulen treatment suppressed T and free androgens to normal in all groups, and raised TeBG more than 350% from the baseline. These data suggest a decrease in androgen production. The effects of dexamethasone and Ovulen on all three groups were similar in *percent* changes. As Group B patients resemble those of Group A biochemically and clinically, except for possibly being less hyperandrogenic, the concept of ovarian hyperandrogenism should be expanded to include patients with no anatomic ovarian abnormality, particularly in milder cases. (AM. J. OBSTET. GYNECOL. 134:445, 1979.)

POLYCYSTIC OVARY SYNDROME (PCO) commonly refers to patients with the clinical features of menstrual irregularity and variable degrees of obesity and hirsutism. This syndrome is characterized biochemically by excessive ovarian secretion of androgens as evidenced by increased levels of androstenedione (A) and testosterone (T) in the ovarian vein plasma and by increased free plasma androgens.[1, 2, 3] Also the testosterone-binding globulin (TeBG) capacity is significantly lower in women with PCO than in normal women.[3, 4] The gross characteristics of the ovaries in this syndrome are typically moderately enlarged, pearly white, sclerotic, and polycystic. There appear to be no unique histologic features of PCO.[5] Although capsular thickening, theca cell luteinization, stromal hyperplasia, and microfollicular "cysts" representing follicles arrested at various stages of development are thought to be histologically characteristic of polycystic ovaries, little information is available to correlate biochemical and histologic parameters.

In the present study we measured the plasma levels of total and free (unbound) androgens and TeBG capacity in patients with the clinical diagnosis of PCO and correlated biochemical parameters with histologic findings. Also the effects of estrogen-progestin on total and free androgens and TeBG were studied.

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Table I. Clinical data on nine patients in whom ovarian histology was available

Case No.	*Age (yr.)*	*Weight (kg)*	*Menstrual status*	*Hirsutism**	*Ovarian histology*
Group A:					
1	23	71	Oligomenorrheic	+++	Thick capsule, theca luteinization
2	26	80	Oligomenorrheic	+++	Thick capsule, extensive stromal luteinization and hyperplasia
3	32	111	Prior total abdominal hysterectomy	++	Thick capsule, multiple cysts, stromal hyperplasia
4	19	71	Oligomenorrheic	++	Thick capsule, multiple cysts
Group B:					
5	28	61	Oligomenorrheic	+++	Normal
6	19	48	Oligomenorrheic	+++	Normal
7	20	104	Oligomenorrheic	+++	Normal
8	26	71.5	Dysfunctional uterine bleeding	+	Normal
9	23	78.7	Oligomenorrheic	+	Normal

*(+) mild, (++), moderate, (+++) marked

Table II. Plasma androgen levels (mean ± SEM) and mean percent changes* before and after dexamethasone and Ovulen suppression

Group	*Test*	*T (ng/100 ml)*	*FTeI*	*FHSI*	*TeBG (μg/L)*
Normal women (normal range)		14-66	3-22	28-110	13-36
A	Control	93 ± 19.1	49 ± 11.4	151 ± 19.5	6 ± 1.3
	Dexamethasone	90 ± 23.6 (−17.7%)	41.3 ± 9.9 (−30.4%)	93.5 ± 6.2 (−36%)	6.1 ± 0.9 (0%)
	Ovulen	41.5 ± 13.9 (−51.6%)	9 ± 2.5 (−80.5%)	64.5 ± 10 (−57.6%)	27 ± 3.9 (+350%)
B	Control	66 ± 10.3	25.5 ± 4.5	117 ± 15.3	10.5 ± 1.3
	Dexamethasone	51.5 ± 11.9 (−22.9%)	20.2 ± 4.5 (−24.3%)	65.8 ± 14.5 (−45%)	9.4 ± 0.5 (−9.5%)
	Ovulen	28 ± 6.3 (−54.6%)	4.5 ± 1.0 (−82.7%)	33.9 ± 8.7 (−70%)	48.4 ± 3.4 (+364%)
C	Control	91.3 ± 18.6	35 ± 6.6	145 ± 11	10.6 ± 1.0
	Dexamethasone	64 ± 11.5 (−33.8%)	22.9 ± 3.5 (−32.7%)	83.3 ± 10.9 (−46.6%)	11.4 ± 1.4 (0%)
	Ovulen	37 ± 3.9 (−50.8%)	6.6 ± 1.3 (−75.5%)	52.4 ± 6.5 (−63%)	53 ± 7.8 (+385%)

*Mean of individual percent changes from control values (in parentheses).

Material and methods

Study subjects. Thirty-one patients with the clinical features of PCO were studied. All patients had biochemical evidence of hyperandrogenism as indicated by elevated plasma levels of T, free testosterone index (FTeI), or free 17β-hydroxysteroid androgen index (FHSI), often with low TeBG capacity.[6] No subject had evidence of any other endocrinopathy, and none had received any hormonal medication for at least one month prior to the study. Baseline blood samples were obtained. The patients were then given dexamethasone, 0.5 mg every 6 hours orally for 3 days. At this time of adrenocortical suppression blood samples were again collected. The patients were then placed on a regimen of mestranol, 0.1 mg, and ethynodiol diacetate, 1 mg (Ovulen*) daily, and they had blood samples drawn between 14 and 21 days of medication. Blood samples were also taken from seven normal women with regular menstruations before and 18 to 21 days after the daily administration of Ovulen. All blood samples were collected between 8:00 and 10:00 A.M. Plasma was separated and kept at −18° C until the time of analysis.

Hormone assays and histologic examination. Plasma T, FTeI, FHSI, and TeBG capacity were determined by competitive protein-binding methods.[6, 7] 17β-Hydroxysteroid androgens are the total ether-extractable substances in plasma which have a high

*Ovulen, G. D. Searle & Co., Chicago, Illinois.

affinity for TeBG; two thirds of these substances in normal women are composed of dihydrotestosterone (DHT), androstenediol, and androstanediol, as well as testosterone.[8] These assay methods possess interassay coefficients of variation of 11%, 11.4%, 6%, and 13% for T, FTeI, FHSI, and TeBG, respectively.

In nine patients, ovarian tissue was available for histologic evaluation (hematoxylin and eosin stain). The tissue samples were obtained by multiple biopsies via laparoscopy in six patients and by wedge resection of the ovaries in two patients. The specimen from one patient was obtained following oophorectomy. The presence of any of the following findings was considered consistent with PCO: thick capsule, thecal luteinization, stromal hyperplasia, and multiple microfollicular cysts.[5] Four patients showed PCO pictures (Group A), and five had histologically normal ovaries (Group B). The remaining 22 patients did not have any tissue available for examination (Group C).

Results

Clinical data. The clinical features and ovarian histology of Group A and Group B are shown in Table I. Except for the histologic findings, there were no clear differences clinically between the groups. Group B patients tended to have less severe hirsutism.

Androgens in normal women. In seven normal women who served as controls, the baseline plasma levels (mean ± SEM) of T, FTeI, FHSI, and TeBG were 46 ± 5.3 ng/100 ml and 9.2 ± 0.5, 62.2 ± 3.9, and 41.9 ± 5.4 μg/L, respectively. Ovulen suppression reduced the mean levels of T, FTeI, and FHSI to 31.2 ± 3.7 ng/100 ml and 1.9 ± 0.5 and 22.8 ± 6.5 μg/L (mean changes of 32.2%, 80%, and 63.3%), respectively. On the other hand, the mean level of TeBG was increased to 82.8 ± 3.6 μg/L. The effects of dexamethasone suppression on these androgen parameters in normal women have been previously reported.[9]

Plasma T (Fig. 1). Although the mean control level of T in Group A was higher than in Groups B and C (Table II), the difference was not significant. With dexamethasone suppression the plasma levels of T fell in Groups A, B, and C (17.7%, 22.9%, and 33.8%, respectively). These changes were not significant. However, with Ovulen suppression, T levels normalized in all groups, decreasing by 50% or more (Table II). These values are significantly different from the control levels. While T levels as a group fell significantly, it is noteworthy that individually some did not show a significant reduction.

Plasma FTeI. In contrast to the levels of plasma T, a significant difference ($p < 0.05$) was noted in the mean control levels of plasma FTeI between Group A and

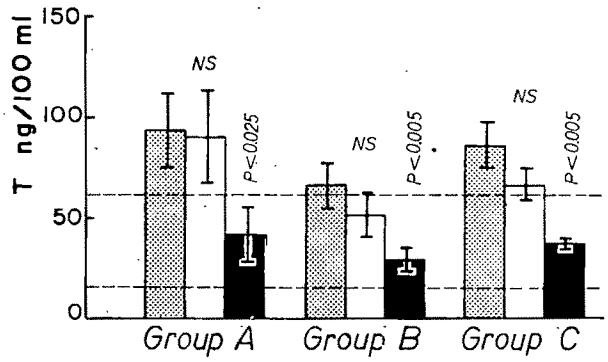


Fig. 1. Plasma levels (mean ± SEM) of total testosterone in three study groups of clinical PCO: Group A (positive histology for PCO), Group B (normal histology), and Group C (histology not studied). The shaded, white, and black bars respectively represent control values and values following dexamethasone and Ovulen suppression. The significance of the change from control was obtained by Student's t test (paired) with one tail. The dotted lines represent normal control ranges. NS: Not significant.

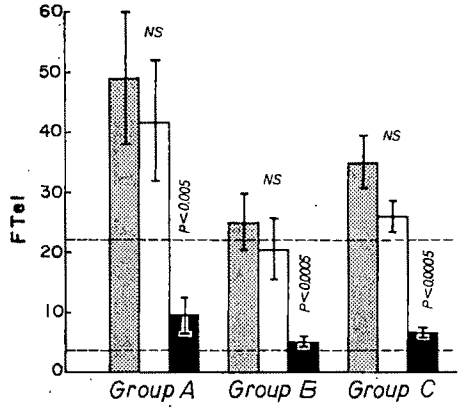


Fig. 2. Plasma levels (mean ± SEM) of FTeI. For explanations see Fig. 1 legend.

Group B (Table II). This is probably related to the lower TeBG levels of Group A. Dexamethasone suppression resulted in decreases of FTeI levels in all groups, although these changes were not significant (Fig. 2). On the other hand, the differences between the control levels and the levels with Ovulen treatment were highly significant in all three groups. The degree of decrease was comparable in all groups, ranging from 75.5% to 82.7%, and Ovulen treatment consistently normalized the levels of FTeI in all individual patients.

Plasma FHSI. The mean control level of Group A was higher, but not significantly, than that for Group B (Table II). As noted in Fig. 3, both suppressive treatments significantly reduced the levels of FHSI in all three groups. The FHSI decreased more than the FTeI and T with dexamethasone suppression (36%, 45%, and 46.6% in Groups A, B and C, respectively). With

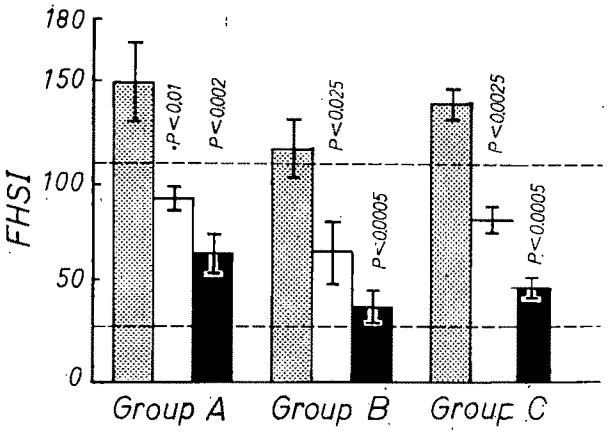


Fig. 3. Plasma levels (mean ± SEM) of FHSI. For explanations see Fig. 1 legend.

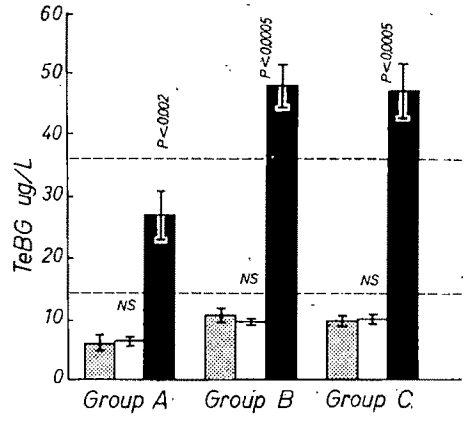


Fig. 4. Plasma levels (mean ± SEM) of TeBG capacity. For explanations see Fig. 1 legend.

Ovulen suppression, the FHSI, just as the FTeI, was again reduced to the normal range. The degree of suppression was the same in all groups (58% to 78%).

TeBG capacity. Plasma TeBG levels in all three groups were below the normal range. The difference between Group A and Group B was significant ($p < 0.025$). With dexamethasone suppression essentially no changes in TeBG levels were noted. However, Ovulen treatment resulted in a marked increase (over 350%) in TeBG levels in all groups (Fig. 4). This significant increase is believed to be due to the estrogenic component of Ovulen.

Comment

Patients with the clinical features of PCO typically have elevated plasma free androgen levels which are not normally suppressed by dexamethasone.[3-9] Assuming that dexamethasone in the dosage used in the study did not affect ovarian function,[9, 16, 17] lack of a significant reduction in FTeI and FHSI with dexamethasone suppression probably indicates the main source of androgens in the study patients to be the ovary.

Polycystic ovaries are typically enlarged, pearly white, sclerotic, and multicystic. However, the gross appearance is variable, as is the symptomatology.[10, 11] Despite numerous studies, there appear to be no unique diagnostic histologic features of PCO.[5, 10] In our nine patients with ovarian hyperandrogenism, defined by the above clinical and endocrinologic criteria, in whom ovarian tissue was available for histologic examination, four showed the histologic features of PCO. The ovaries of five patients were histologically normal. Although multiple biopsies might not have been representative of the entire ovaries, the findings suggest that ovarian hyperandrogenism can be associated with histologically normal ovaries.

The baseline free testosterone level in Group A patients (with PCO histology) was slightly higher ($p < 0.05$) than in Group B patients (with normal histology), although the difference in the FHSI was not significant. Therefore, it is possible that the amount of ovarian androgen production may parallel the degree of histologic change. Since it has been shown that the stromal compartment is the major source of androgen production in the ovary,[12] obvious stromal change might be expected to correlate with androgen levels.

All study groups showed low TeBG. This finding is in agreement with previously reported findings.[3, 14] Since obesity is commonly associated with low TeBG capacity, it may be partly related to the difference in TeBG levels between Group A and Group B.[3, 13] TeBG is a major determinant of androgen binding in plasma, the percentage of free testosterone being inversely related to the TeBG levels and representing the biologically active moiety.[6] High levels of FTeI and FHSI are the results of increased production of androgens and low TeBG capacity.

The pharmacologic effects and clinical significance of dexamethasone suppression in hyperandrogenic conditions should be interpreted with caution because of various controversial reports.[15, 16, 18] Several studies have shown that pituitary-ovarian suppression was more effective than pituitary-adrenal suppression in the treatment of hirsutism.[18-20] Our data provide an explanation for this by indicating that plasma free androgens are more markedly depressed by this treatment than are total plasma androgens.

The significant reduction of plasma T and FTeI (50% and 75.5%, respectively) levels in our patients during Ovulen treatment is obviously greater than the changes during dexamethasone suppression. Suppression of plasma T of a similar magnitude has been reported in women with PCO using other sex steroids.[21-23] The fact that plasma T levels decreased in

the presence of elevated TeBG indicates a reduction in T production since TeBG is a major determinant of T metabolism,[8] and this agrees with other investigations.[9, 20] The marked reduction of FTeI and FHSI then is probably due to decreased ovarian production of androgens and increased levels of TeBG capacity. The magnitude of suppression of plasma T, FTeI, and FHSI levels during Ovulen treatment was similar between Group A and Group B. This finding suggests that histologically normal ovaries can be the major source of ovarian hyperandrogenism. It is noteworthy that with Ovulen suppression the magnitudes of percent changes of T, FTeI, and FHSI levels in the study patients were comparable to those in normal control women; however, the levels of free androgens remained considerably higher than those in normal women. One should interpret the response of plasma androgen levels to estrogen-progestin treatment with caution as there is a question of some suppressive effects of estrogen-progestin on the pituitary-adrenal axis.[24, 25]

In all patients in the study, Ovulen treatment induced a marked increase in the levels of TeBG capacity (over 350% increase). It reflects the effect of estrogen component. Givens and associates[20] reported a similar finding using other estrogen-progestin combination. The effectiveness of raising the plasma TeBG levels appears to be variable, depending on the amount of estrogen and the type of progestin given.[20, 26]

The data presented suggest that the ovary is the source of hyperandrogenism in hirsute, oligomenorrheic patients in whom dexamethasone suppressibility is poor. Furthermore, Group B patients are identified as having an entity which clinically, biochemically, and functionally resembles Group A (PCO) but has normal ovarian histology. Therefore, the concept of ovarian hyperandrogenism should be expanded to include patients with no anatomic ovarian abnormality. Group A (PCO) and Group B (variant of ovarian hyperandrogenism with normal histology) may differ only in the degree of hyperandrogenism and ovarian histology. In view of the good correlation between the levels of luteinizing hormone (LH), androstenedione, and T during ovarian suppression and recovery from such suppression,[20] this difference may depend on the degree and chronicity of inappropriate LH secretion.[27] The results of the study show that estrogen-progestin preparations are more effective in correcting ovarian hyperandrogenism than expected from the measurement of plasma total T levels.

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Discussion

Dr. Richard F. Mattingly, Milwaukee, Wisconsin. This is a very interesting, detailed, and sophisticated study of androgen metabolism.

This study of 31 women with elevated plasma androgen levels adds further information to the increasing body of knowledge of androgen biosynthesis and distribution. The authors have utilized an advanced radio-

immunoassay technique in measuring plasma T, FTeI, and FHSI as well as the TeBG capacity in this group of hirsuit women. All of this is highly technical work, which gives credence to the authors' findings.

This study represents an attempt by knowledgeable investigators to correlate biochemical events in steroid metabolism with histologic changes in the ovary. Their message to us today, following an elaborate metabolic study of various free and bound plasma androgens, is that the ovary is the source of the excess androgen in this group of cases and that the concept of ovarian hyperandrogenism should be expanded to include a group of women with histologically normal ovaries.

While these conclusions may be correct, one must question whether or not there is sufficient evidence in this study to substantiate this theory. Indeed it is our proposal that this report may be somewhat premature and that further studies will be required to clarify these preliminary observations.

Basically, the study of ovarian tissue in only nine of 31 cases (29%) provides much too limited histologic information to draw any conclusions regarding the androgen function of normal ovaries in hirsuit women. More importantly, the authors attempted to further divide their study of these nine cases into two groups (A and B) and those that showed no histologic abnormality (five cases). We submit that this division of cases is somewhat artificial since laparoscopic biopsy of the ovarian cortex provides only limited histologic information and may completely exclude the important medullary components of the gonad.

It would be difficult to say that the normal ovaries do not contain areas of hyperthecosis. This condition was originally described by Frankel (1943) and without a medullary biopsy this diagnosis can be made only by wedge resection.

The differential diagnosis between the so-called PCO and hyperthecosis is important in that there is much more virilization and a significant degree of androgen excess in the hyperthecosis ovary, and these ovaries do not respond well to clomiphene stimulation of ovulation. Such cases are always associated with hirsutism and with mild virilization.[1]

In contrast, only 50% of the cases with PCO will show hirsutism.

We are also concerned about the interpretation drawn from this brief, 3 day course of adrenal suppression with low-dose dexamethasone. Most investigators in the field have extended the adrenal suppression period for a minimum of 5 days and, more frequently, for a period of 7 days. We have not used the 2 week dexamethasone suppression test as advocated by Abraham and Busher,[2] but we are mindful of the fact that normal plasma levels of cortisol (F) do not provide conclusive evidence of complete suppression of the zona reticularis of the adrenal cortex. More conclusive information of adrenal suppression is available by measuring dehydroepiandrosterone sulfate, a "prehormone" which is excreted almost exclusively by the adrenal cortex. The fact that there was no statistically significant suppression of plasma androgens in this study, using a 3 day, low-dose dexamethasone technique, indicates that longer suppression studies are necessary before the adrenal source of androgen excess can be excluded. This, of course, is very important since the clinical management of patients with an adrenal source of androgen excess is much more difficult than that of patients with an ovarian source. We are also reluctant to rely on the levels of free 17β-hydroxysteroids as a sensitive monitor of androgen excess since this assay contains what we call a "mixed bag" of plasma androgens and may indeed mask the subtle rise in dihydrotestosterone (DHT) and their clinical effect on hirsutism. DHT levels would need to be elevated as much as four times according to Abraham and Busher[2] in order to increase this 17β-hydroxysteroid level to any significant clinical degree. We would be interested to know why the authors chose this specific assay in preference to measuring DHT.

This is an interesting study of a very complex problem of androgen dynamics. Distinct advances have been made in the past decade which more clearly define the specific hormones or "prehormones" that are involved in androgen metabolism and hirsutism. These advances have been made by the availability of sensitive radioassay studies. In the clinical interpretation of these highly sophisticated steroid studies, one must be cautious to avoid drawing conclusions from limited studies. In this regard, the hypothesis that androgen excess may be produced in normal ovarian tissues is an attractive, but as yet unproved theory since only one of the five cases with normal ovarian biopsies had adequate tissue for histologic interpretation.

To accept this theory would require histochemical evidence of a defect in the conversion of androgens to estrogens in a histologically normal-appearing ovary, as is seen occasionally in the conversion of testosterone to estradiol. There is a specific syndrome, 17β-reductase deficiency, in which this occurs, but we question if all these cases had this particular problem.

It may be preferable to combine the groups of cases and data, as well as the observations noted in the ovarian biopsies. When further studies are available, which include wedge resection of the ovaries, to determine the presence or absence of hyperthecosis, a more definitive statement can be made regarding the correlation of ovarian histology and ovarian hyperandrogenism.

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DR. GEORGE D. WILBANKS, Chicago, Illinois. Dr. Kim and his associates have presented some very interesting data from 31 patients with clinical features of PCO, 27 of whom possibly did not have ovaries that were "polycystic." They classified these patients by biochemical "ovarian hyperandrogenism" rather than by histologic changes in the ovary. The authors have added some valuable information on this perplexing syndrome (or syndromes) but there still remain significant questions as to the contribution of adrenal androgens to the disease process.

The etiology of polycystic ovaries has been the subject of considerable discussion in the literature.[1] The role of the hypothalamus, the involvement of the ovaries, and the probable involvement of the adrenals are widely discussed problems. In most cases such patients may have, in addition to the polycystic ovaries, the typical clinical syndrome characterized by hirsutism, menstrual irregularities, and infertility. Such a clinical syndrome, however, is not necessarily associated with "polycystic ovaries" as this study shows. It seems more important to determine whether in such a syndrome there is hyperandrogenism rather than to start with the enlarged ovaries. This study, with good laboratory evaluation, proves that in all such patients one can document hyperandrogenism.

The next problem is to determine the source of the hyperandrogenism. There have been conflicting reports in the literature as to the relative role of the ovary and adrenal, which may reflect methodology and types of tests used rather than actual gland involvement.[2, 3] For example, certain studies by adrenal and ovarian vein catheterization suggest the ovary to be primarily involved; many others, utilizing adrenal suppression or stimulation tests, have suggested significant involvement of the adrenal, alone or in combination with the ovary.

The authors' study suggests that hirsutism is an ovarian problem. The method utilized depends on measuring (1) plasma T, (2) the FTeI, and (3) the free 17β-hydroxysteroid index. The 17β-hydroxysteroids are T, DHT, androstenediol, and androstanediol. Androgens like androstenedione, dehydroepiandrosterone (DHEA), and dehydroepiandrosterone sulfate (DHEA-S) are not measured by this method. The above methodology is based on the assumption that an index of the free androgen portion, i.e., the biologically active one, would be more meaningful. Rosenfield[4] has shown over the years that one can indeed document hyperandrogenism by much methods in patients with normal total T levels, who otherwise would have been considered normal. The reported results, however, may not conclusively indicate that the adrenal is not involved in that the 3 day dexamethasone suppression test is not long enough to adequately suppress adrenal androgen function, although it may suppress corticosteroid function. Had the suppression been longer, the observed drop may have been greater in these patients. Second, the observed lowering of androgens by Ovulen does not necessarily imply ovarian suppression because the increase in binding globulin leads to an increase in cortisol and a subsequent drop of adrenocorticotropic hormone which results in a drop of adrenal androgens.[5] The fact that patients with normal ovaries and those without biopsy showed a greater dexamethasone suppression may also support this point, i.e., that the patients with histologically "normal" ovaries and ovaries not examined had a significant adrenal component. Third, since DHEA-sulfate was not measured, a significant adrenal androgen component was not determined. Would Dr. Kim please comment on these points.

If indeed the measurement of these biochemical parameters indicates that there is no special diagnostic clinical features for patients with truly histologic polycystic ovaries and those with normal histology, this would eliminate the need for ovarian biopsies in establishing the diagnosis. If Ovulen treatment is effective in decreasing the hyperandrogenism in these patients, this would certainly simplify the treatment. Did the Ovulen treatment retard the hirsutism? Finally, if indeed these tests do indicate a primary ovarian involvement, are there specific clinical signs and symptoms, such as menstrual irregularity, anovulation, and infertility, that characterize this variant of the syndrome?

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DR. JAMES A. MERRILL, Oklahoma City, Oklahoma. I think the authors have done an excellent job of illustrating that the critical issue is to identify patients with a syndrome of anovulation and hyperandrogenicity, determine from measurement of various biochemical parameters the probable origin of the biochemical defect, and then hopefully correct it. If one studies the morphology of the ovary, it will be found that those characteristics described as being typical of PCO may be found in a variety of related and unrelated disorders, including injuries to the central nervous system and spinal cord injuries, just to mention a few.

I think that the time when gross and microscopic

pathology of the ovary should be considered a cardinal feature in the diagnosis and/or treatment of this clinical syndrome has been gone for a long time. What Dr. Kim has said here today simply re-emphasizes that point and does so, in my opinion, in a very fine way.

DR. EDUARD EICHNER, Cleveland, Ohio. I have had a couple of patients with Stein-Leventhal ovaries who under stimulation of Clomid and gonadotropins apparently ovulated with the basal body temperature showing a normal ovulatory phase. When pregnancy failed to occur, wedge resection of the ovaries was carried out and under the microscope none of the specimens had a corpora albicans. This means that even though we had endometrium that suggested ovulation and basal body temperature that suggested ovulation, ovulation apparently had not occurred. Both of these patients became pregnant after wedge resection and were delivered at term.

DR. KIM (Closing). The last comment made by Dr. Merrill was indeed very important as one of the points in this study was to show that histologic evaluation or laparoscopic visualization of the ovaries really adds little in terms of making a diagnosis of ovarian hyperandrogenism and formulating a therapeutic approach. It is primarily a biochemical abnormality and is best dealt with biochemically.

Drs. Mattingly and Wilbanks had several important comments and questions. As to the question of biopsy not representing the entire ovaries, it is obviously an inevitable disadvantage of any form of biopsy. However, any possibility of misrepresenting the ovaries would have been smaller when multiple biopsies were taken. Certainly deep stromal tissue could have been missed. As far as the length of dexamethasone suppression is concerned, we are interested in the diagnostic application of such treatment. It is logical to find out if the population in study is different from the normal population. We have reported previously that in normal women dexamethasone suppression for 3 to 4 days would suppress not only the cortisol level but also most of the androgenic parameters studied. Therefore, we elected to use a 3 day suppression. As mentioned by Dr. Mattingly, it may take longer than 4 days to see any therapeutic effects of dexamethasone. For a diagnostic purpose the 3 to 4 day suppression would be adequate and informative as shown in this study.

Dr. Mattingly suggested the measurement of dehydroepiandrosterone sulfate (DHAS). Certainly it is the most abundant circulating androgen but the biologically least potent one. It is mainly from the adrenals, serving as a precursor, and has a very little significance in clinical androgenicity. Therefore, we limited hormone measurements to the biologically potent androgens. The reason for measuring the plasma FHSI was based on our previous studies that it represented the unbound 17β-hydroxysteroid androgens. A total of 75% of 17β-hydroxysteroid androgens in plasma, dihydrotestosterone, androstenediol, and the isomers of androstanediol, in addition to testosterone, would be measured in our assay. It represents an overall androgenic picture.

Dr. Wilbanks raised a practical question whether or not the estrogen-progestin treatment did improve hirsutism. Although I have no data to support it, my impression is that some of the patients did show clinical improvement. Documentation of clinical improvement of hirsutism parallel to biochemical improvement in a large series of cases should be done. As to the question of the primary ovarian involvement as a cause of ovarian hyperandrogenism, I do not think this is the case. The studies have shown that inappropriate LH/follicle-stimulating hormone secretion is operational as a cause of the syndrome. Our data simply indicate that ovarian hyperandrogenism, when encountered, is probably a gonadotropin-dependent condition rather than a primary ovarian disease. Regarding whether or not the adrenal components were ruled out, I cannot say that they were. Although there have been some studies suggesting a possible suppressive effect of oral contraceptive pills on adrenocorticotropic hormone–dependent adrenal function, it is probably not the case in ovarian hyperandrogenism. Because of an increase in the corticosteroid-binding globulin level during oral contraceptive treatment, one finds elevated cortisol levels which may affect adrenocorticotropic hormone–dependent adrenocortical function. But in our study the levels of T and TeBG behaved quite differently, suggesting that the adrenal component, if any, was negligible.

Stage I squamous cell cancer of the vulva

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A review of 106 patients with Stage I squamous cell cancer of the vulva treated at the Mayo Clinic from 1950 through 1975 is presented. Microinvasive lesions (5 mm penetration or less) were present in 96 patients (91%); invasive lesions (more than 5 mm penetration) were diagnosed in 10 (9%). Inguinal node involvement was present in nine patients (8.4%); one of these also had pelvic node involvement. Recurrence developed in 13 patients (12%). Four patients experienced inguinal node metastasis after initial surgical therapy. The incidence of positive nodes among patients with lesions invading the stroma for 3 mm or less was 3%. Thus, individualization for inguinal lymphadenectomy may be possible according to the age and condition of the patient when the depth of invasion is 3 mm or less. (AM. J. OBSTET. GYNECOL. 134:453, 1979.)

STAGE I SQUAMOUS CELL CANCER of the vulva[1] includes lesions, confined to the vulva, of 2 cm or less in largest diameter, in the absence of palpable, or with palpable but not clinically suspicious, lymph nodes in the groin (T1N0M0; T1N1M0). There is no general agreement regarding the extent of surgical therapy suitable for patients who have such lesions. Attention has been paid to the histologic features of the lesions[2, 3] as a basis of selecting patients for whom dissection of nodes can be avoided. However, several reports tend to indicate that early invasive carcinoma of the vulva may not behave like its counterpart in the cervix and that lymphadenectomy should be included in the initial therapy.

This study was designed to evaluate clinical and histologic factors that may affect prognosis and to outline a therapeutic approach for patients who have Stage I squamous cell cancer of the vulva.

Material and methods

The records of 693 patients with vulvar malignancy seen at the Mayo Clinic from January 1, 1950, through December 31, 1975, were reviewed. Vulvar lesions 2 cm or less in size were present in 151 patients. Excluded from this group were patients with vulvar malignancies other than epidermoid carcinoma (19), recurrent (seven) or metastatic (two) tumors, other concomitant pelvic malignancies (one), suspicious inguinal nodes (one), extension into the vagina, urethra, or perineum (seven), lesions with doubtful invasion (two), and cases with no available tissue slides (six). All patients were staged retrospectively according to the criteria of the International Federation of Gynecology and Obstetrics.[1] Stage I squamous cell cancer of the vulva was diagnosed in 106 patients, and these patients constitute the material for this study.

The records of these patients were reviewed for age, symptoms, and duration of symptoms, associated illnesses and vulvar diseases, previous medical vulvar therapy, treatment, recurrences, and outcome. Particular attention was paid to size, site, and number of lesions and to lymph node involvement. The slides from surgical specimens or preoperative biopsies (if excisional) were reviewed in all patients with reference to depth of invasion, tumor cell type, tumor differentiation, microscopic confluence, and vascular and lymphatic permeation.

Depth of invasion was measured from the surface of the squamous epithelium. If an ulcerated lesion was present, it was measured from the surface of the adjacent epithelium. Microinvasion was said to be present when there was 5 mm or less of stromal penetration and invasion, when penetration was more than 5 mm.

From the Mayo Clinic and Mayo Foundation.

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Table I. Surgical procedures

Procedure	*No.*
Radical vulvectomy with bilateral groin node dissection	34
Radical vulvectomy with bilateral groin and pelvic node dissection	34
Radical vulvectomy with second-stage groin node dissection	3
Radical vulvectomy	10
Simple vulvectomy	17
Hemivulvectomy	2
Wide local excision	3
Local excision	3
Total	106

Confluence was defined as a group of tumor cells filling an area of 2 mm or more. A group of tumor cells surrounded by a definite endothelial lining was considered lymphatic permeation; the presence of blood elements was an essential requirement for the diagnosis of vascular permeation.

We have considered recurrence to be those lesions arising in a previously excised area—vulva, groin, or pelvis. Postoperative metastases are lesions arising in a previously untreated area, either groin or pelvis.

Results

Age and symptoms. The age of the patients ranged from 30 to 87 years (mean, 61 years). Thirty-three patients were nulliparous. Pruritus was the most common presenting symptom in 79 patients (75%). Other presenting symptomatology included ulceration in 58 patients (55%), tumoral induration or mass in 43 (41%), pain in 26 (25%), and bleeding in nine (8%).

Duration of symptoms was less than 1 year in 40 patients (38%) and 1 or more years in 66 (62%). Fourteen patients (13%) had symptoms for more than 10 years. Duration of symptoms did not correlate with size of the lesions, lymph node involvement, recurrences, or survival.

Associated illnesses. Associated illnesses included hypertension in 22 patients, diabetes in eight, thyroid disease in seven, skin diseases in six, and rheumatoid arthritis, multiple sclerosis, and chronic ulcerative colitis in one patient each.

Associated malignancies. Previous or subsequent malignancies occurred in 28 patients; they included seven cervical, six mammary, three uterine, two ovarian, two cutaneous, and two rectal lesions, and one case each involving the colon, anus, esophagus, tongue, larynx, and vagina (carcinoma in situ).

Associated vulvar diseases. Associated vulvar diseases were present in 85 patients (80%). They included vulvar dystrophy in 74 (70%) (atrophic in nine, hypertrophic in 41, and unspecified, when no previous biopsies were available, in 24), carcinoma in situ in 24 (23%), dysplasia in three (3%), and chronic vulvovaginitis in six (6%). None of the patients had venereal vulvar disease.

Of the 24 patients with coexisting in situ cancers, 16 had a single in situ lesion and eight had two or more lesions. In one of these patients an invasive recurrence developed. There were no in situ recurrences. None of these patients died of vulvar carcinoma.

Before the diagnosis of vulvar malignancy, 50 patients had medical treatment for vulvar symptomatology. Duration of the treatment ranged from less than 1 year in 58 patients to 20 years in three patients (mean, 5.1 years).

Treatment. Table I lists the surgical procedures. Radical vulvectomy was performed in 81 patients (76%), bilateral groin node dissection in 71 (67%), and bilateral inguinal and pelvic node dissection in 34 (32%).

Site of lesion. The right vulva was the most frequent site of the lesion, being involved in 49 patients (46%). The right labia minora and majora were involved in 31 and 28 patients, respectively. Other sites included left vulva in 28 patients (labia minora in 18, labia majora in 10), clitoris in 15, fourchette in 11, and perineum in two. Inguinal lymph node involvement correlated with the site of the lesion as follows: six of 28 patients with left vulvar lesions, one of 49 patients with right vulvar lesions, one of 15 patients with clitoral lesions, and one of 11 patients with fourchette lesions. Patients with right vulvar lesions had a significantly ($p < 0.05$) lower incidence of nodal involvement than did those with left vulvar lesions. There was no difference relative to survival rate. The only patient who had positive pelvic nodes had a lesion in the left labia majora.

Number of lesions. Multiple lesions existed in 10 patients, four patients having had two lesions, and six, four or more lesions. All of these tumors were microinvasive. None of these patients had positive nodes; one had a recurrence and another died as a result of vulvar cancer. There was no statistically significant difference ($p > 0.2$) relative to survival when these patients were compared with patients who had one lesion.

Size of lesion. Lesions smaller than 1 cm were present in 20 patients; lesions measuring 1 to 2 cm were present in 86 patients. All lesions smaller than 1 cm were microinvasive and were grade 1 or 2. Four had microscopic confluence and one showed lymphatic permeation. None of these patients had positive nodes or died of the malignancy. However, two had inguinal node metastases postoperatively and three experienced vulvar recurrence.

Among patients with lesions measuring 1 to 2 cm, nine (10.4%) had nodal metastases, 10 experienced vulvar recurrence, and four died of the disease. Microscopic confluence was noted in 36 lesions and lymphatic permeation in eight; tumor differentiation ranged from grade 1 to grade 4. The only patient with an anaplastic tumor (grade 4) had a 2 cm lesion. There was no statistically significant difference ($p > 0.4$) relative to survival between patients with lesions smaller than 1 cm and those with lesions 1 to 2 cm in size.

Nodal involvement. Inguinal node involvement existed in nine patients (8.4%). All except one underwent pelvic node dissection. One had positive pelvic (obturator and common iliac) nodes. This patient had a grade 2 lesion, 1.5 cm in size, with 5 mm of stromal invasion, microscopic confluence, and no lymphatic permeation. She died of vulvar cancer 6 months after surgery. Another patient with positive inguinal nodes died of intercurrent disease. The remainder are still alive and free of disease. The corrected 5 year survival rate for patients with positive nodes was 88.8% as compared with 97.9% for those with negative nodes. However, this difference was not statistically significant ($p > 0.1$). None of the patients with positive nodes experienced inguinal recurrence. Vulvar recurrence developed in one of nine patients who had positive nodes and in 12 of 97 with negative nodes.

Nodal metastases were ipsilateral in five patients and contralateral in four (two had lesions in the labia minora and two had lesions involving one side of the clitoris). The number of nodes involved ranged from one to five (mean, 2.1).

Depth of penetration. Histologic examination of the lesions revealed microinvasion (5 mm or less of penetration) in 96 patients (90%); nine of these patients had nodal involvement. Ten patients experienced vulvar recurrence, three had inguinal metastases (two with 2 mm of invasion and one with 5 mm of invasion), and three died of the disease (Table II).

Lesions that invaded the stroma for less than 2 mm showed no microscopic confluence and no lymphatic permeation. Among these patients, none had positive nodes and none died of the disease. One patient experienced a vulvar recurrence.

Invasion (more than 5 mm of penetration) was present in 10 patients (9.4%). None of them had positive nodes. Vulvar recurrence occurred in three patients, and one of these also had an inguinal recurrence. Inguinal node metastasis developed in one patient, who died of the disease.

Microscopic confluence. Microscopic confluence, as previously defined, was observed in 40 lesions (38%). Nodal metastases existed in six (15%) of these patients, whereas it occurred in three patients (5%) among those who did not have microscopic confluence. However, this difference was not statistically significant ($p > 0.2$). Among patients with lesions showing confluence, four died as a result of vulvar cancer. The difference was significant ($p < 0.01$) when compared with patients who had lesions without confluence.

Table II. Depth of penetration (millimeters) correlated with inguinal node involvement, survival, and development of inguinal node metastases postoperatively

Invasion (mm)	*No. of patients*	*No. of positive lymph nodes*	*No. of patients who died*	*No. with metastases*
1	19	0	0	0
2	26	1	0	2
3	23	1	1	0
4	16	4	0	0
5	12	3	2	1
>5	10	0	1	1
Total	106	9	4	4

Lymphatic permeation. Permeation of lymphatic channels was observed in nine patients. Two of these patients had positive nodes, whereas seven of the patients with no lymphatic permeation had positive nodes. One patient died of vulvar cancer and one experienced vulvar recurrence. There was no statistically significant difference relative to nodal involvement, recurrence, and survival between these groups of patients.

Vascular permeation. Permeation of vascular channels was not identified in any of the lesions studied in the present series of patients.

Tumor cell type. Large cell, keratinizing-type tumors were present in 89 patients (84%), large cell, nonkeratinizing in 12 (11%), and large cell, mixed keratinizing in five (5%). There was no correlation between lymph node involvement, survival, and recurrence and the type of epidermoid tumor.

Tumor differentiation. Tumor differentiation (Broders' classification) was distributed as follows: grade 1, 12 lesions (11%); grade 2, 79 lesions (75%); grade 3, 14 lesions (13%); and grade 4, 1 lesion (1%). Positive nodes were present in seven patients (9%) with grade 2 lesions and in two patients (14%) with grade 3 lesions. Among four patients who died, three had grade 2 lesions and one had a grade 4 lesion. In this particular patient, lymphatic permeation and confluence were present.

Follow-up. The clinical course subsequent to primary treatment was observed for 5 years or more in 76 patients, for 10 years or more in 47, and for 20 to 25 years in 10.

Recurrence. Invasive vulvar recurrence, as previously defined, occurred in 13 patients (12%). One additional patient experienced an in situ recurrence. The interval between surgery and recurrence ranged from 6 months to 11 years (mean, 6.4 years). None of the histologic and clinical parameters analyzed was found to correlate with vulvar recurrence.

Inguinal recurrence developed in one of 71 patients who underwent groin node dissection. This patient also had a vulvar recurrence. Inguinal nodes were negative at the time of original surgery.

Recurrence of vulvar dystrophy occurred in 33 patients (45%) among 74 with preoperative dystrophy. Two additional patients had vulvar dysplasia and another, carcinoma in situ.

Metastasis. Among 35 patients with no previous inguinal lymphadenectomy, four had biopsy-proved inguinal node metastasis—three within 3 years and one, 10 years after primary treatment. Three of these four patients also had vulvar recurrence. The original lesion was microinvasive in three of these patients (2 mm in two, 5 mm in one) and invasive in one. Two of these patients had lesions smaller than 1 cm, two showed microscopic confluence, and none demonstrated lymphatic permeation. All lesions were grade 2. One patient died as a result of vulvar cancer, two died of other causes but with tumor present, and the fourth, in whom the cause of death was unknown, had no tumor recurrence.

Treatment of recurrence and metastasis. Treatment of recurrence or inguinal metastatic disease included surgical resection in 11 patients and radiotherapy in three. Three of these patients died as a result of vulvar cancer from 3 months to 11 years (mean, 4.6 years) after secondary therapy. Two patients died of other causes but with cancer of the vulva present.

Survival. Cancer of the vulva was the cause of death in only four patients. Two died 6 and 9 months after the original treatment, one after 4 years, and another after 21 years. Twenty-four patients died of causes other than vulvar carcinoma; two had recurrence of tumor at the time of death. The cause of death was unknown in six patients; one of them had vulvar recurrence. Seventy-two patients are alive and free of disease. The corrected 5 year survival rate was 97.1%.

Comment

The epidemiologic factors among patients in the present series are similar to those for patients with all stages of vulvar carcinoma. Previously reported data relative to age,[4, 5] associated malignancies,[3, 4, 6] associated vulvar dystrophy,[5–9] and carcinoma in situ lesions[4, 7] compare favorably with those from our patients.

The distribution of the lesions was similar to that found by Figge and Gaudenz,[6] the right vulva being the site most commonly involved. These patients had a significantly lower incidence of nodal involvement, but their survival rate was similar to that in patients with lesions of the left vulva.

Multicentric lesions have been reported[7, 9] in an even higher percentage of patients than that found in this series. The number and size of the lesions were not significant prognostic factors in the present series of patients.

Inguinal node involvement was present in 8.4% of patients. Previously reported incidences of involvement for Stage I vulvar malignancies have ranged from 10.5% to 31%.[6, 10] Positive nodes were present only in patients who had lesions measuring 1 cm or more and in those with a depth of penetration of 2 mm or more. However, two patients with lesions smaller than 1 cm had inguinal node metastases postoperatively.

Microscopic confluence, lymphatic permeation, and tumor differentiation were not prognostic factors relative to nodal involvement. Microscopic confluence correlated significantly with patient survival, whereas lymphatic permeation and tumor differentiation did not. However, anaplastic lesions (grade 4), which are rare, seem to have an unfavorable prognosis. The only patient with an anaplastic tumor died as a result of vulvar cancer. Parker and associates[3] reported a similar case.

In the present series, the margins of excision appeared to be free of malignancy in all specimens, and therefore this is not a factor to take into account when examining recurrence in our patients. None of the clinical and histologic factors analyzed showed significant correlation with the development of vulvar recurrence. The prevention of vulvar recurrence still remains an unsolved problem for patients with complete excision of the lesions.

The high recurrence rate of vulvar dystrophy after vulvectomy, as demonstrated in this series and others,[6] indicates that dystrophic changes may develop in the site of a previously excised vulva.

Inguinal node metastases occurred in four patients after initial therapy. No correlation was found with the clinical and histologic characteristics of the lesions. One of these patients died as a result of vulvar cancer despite surgical therapy. Previously reported cases[11–14] tend to indicate that these patients have an unfavorable prognosis.

The incidence of inguinal node metastasis after initial surgical therapy, including inguinal lymphadenec-

tomy, was lower than that for patients who did not have initial dissection of nodes. Although the number of patients is small, this finding suggests that inguinal node dissection, as part of the initial therapy, would be helpful in preventing postoperative inguinal node metastases.

This study and previous reports[3, 10–15] tend to indicate that microinvasive cancer of the vulva behaves differently from its counterpart in the cervix and that nodal involvement or postoperative metastasis to nodes does occur in lesions with 2 mm or more of penetration. Therefore, it seems that if treatment or prevention of nodal metastasis is the goal in all patients, inguinal lymphadenectomy should be included in the initial therapy of Stage I squamous cell cancer of the vulva with stromal invasion of 2 mm or more. However, since the incidence of nodal involvement among patients with 3 mm or less of invasion is approximately 3%, individualization of treatment as far as inguinal lymphadenectomy is concerned can be considered according to the age and general status of each patient.

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Discussion

DR. JAMES A. MERRILL, Oklahoma City, Oklahoma. The topic that has received and is receiving considerable attention currently is the treatment of *early* vulvar cancer. For many years the treatment of invasive vulvar cancer has been considered as a single entity and the method of treatment reasonably well standardized. In recent years, people have started to pay attention to the treatment of the early lesion with a view toward the possibility of individualizing treatment of patients with early lesions for the purpose of diminishing the morbidity associated with the disease and its treatment while not sacrificing curability. This review of 106 patients does little to clarify that topic for us, but it does indicate that attention is being given to the possibility of individualization.

Papers have been presented concerning the study of early lesions—Stage I with less than 5 mm of invasion beneath the surface—which have been associated with no lymph node metastases. The authors of those papers have suggested that, in selected instances of early disease, one might reasonably approach the treatment of the disease by radical vulvectomy alone without dissection of the nodes in the groin. Others have reviewed the same category of patients and have found positive groin lymph nodes in approximately 5% of patients. However, at least in one study it was shown that the bulk, if not all, of the cases in which positive lymph nodes were present were in patients whose tumors were anaplastic and in which there was microscopic evidence of vascular invasion. From this they concluded that certain groups of patients with early invasive vulvar cancer might satisfactorily be treated by radical vulvectomy alone, omitting the groin dissection except in those cases in which there was invasion deeper than 5 mm or the lesion was anaplastic or there was microscopic invasion of vascular channels.

I hope that we may learn some categories or definitions that will permit some degree of individualization. The most innovative approach to the management of early invasive cancer was that reported by DiSaia and associates.[1] Their proposal is to select patients carefully: young patients, patients with early lesions, patients whose depth of invasion is less than

5 mm. They have pointed out that the superficial inguinal lymph nodes can be considered as sentinel nodes for the metastasis of vulvar cancer. Thus, a sampling of these superficial inguinal nodes, above the cribriform fascia, is a reasonable method of assessing whether or not groin metastases are present. Their proposed procedure is to remove the superficial inguinal nodes (the sentinel nodes), to examine them by frozen section, and in those cases in which the nodes are negative to do nothing further to the groin and, moreover, to treat the minimally invasive vulvar lesion by a wide local excision. The results in 20 patients are quite good, albeit the follow-up has been relatively short. What is most impressive is the relative infrequency of sexual dysfunction in patients so treated.

I have several questions that I wish to ask the authors. I note that approximately 30% of the 106 patients had pelvic node dissection as part of the therapy. I would wonder what the indications were for pelvic node dissection in that 30% of cases.

I also note a 12% incidence of vulvar recurrence. That seems to me a moderately high figure, and I would ask if the authors have any explanation for that local recurrence rate. Did it have to do with the nature of the original operative procedure? Did it have to do with the known occurrence of multicentricity of this disease which can be not only spatial but also temporal? Were these recurrences multicentric sites in the temporal sense of the word.

I wonder if he could speak to a possible explanation of the apparent difference in node involvement on the two sides of the body.

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DR. JOHN G. MASTERSON, Maywood, Illinois. This is a comprehensive analysis of the clinical and pathologic features associated with the management of 106 Stage I squamous cell carcinomas of the vulva during a 25 year period at the Mayo Clinic. The authors stated that an additional 45 patients with vulvar lesions 2 cm or less were excluded, including 19 with other histologic types of primary carcinoma of the vulva. Therefore, it would appear that their institution had a total of 125 Stage I carcinomas of the vulva during 1950 to 1975. During a comparable period, I managed 49 cases of Stage I carcinoma of the vulva including four malignant melanomas and adenocarcinomas. The mean age of 61 in the authors' series as well as the incidence of associated diseases such as hypertension, diabetes, and positive nodes are lower than that cited in previous reviews, but in the latter all of the four clinical stages of the disease were included. However, the high incidence of associated malignancies and vulvar disease as well as a long delay in the establishment of the diagnosis of vulvar cancer after the onset of the patient's symptoms and signs have again been borne out in this study as in earlier reports in the literature.

However, I was surprised by what I would construe to be a high incidence of local recurrence, namely, 12.27%, even though it did not appear to significantly affect 5 year survival data. Since only 64 percent of the patients in this series had a radical vulvectomy with either a bilateral groin dissection or a bilateral groin dissection and pelvic node dissection, I would be interested in knowing whether the incidence of local recurrence in the group so treated was the same as in 36% who had less extensive procedures. The authors have clearly shown that the incidence of inguinal recurrence is eight times higher in patients who do not have a groin dissection as part of their primary therapy.

The development of recurrent dystrophy in 44.5% of patients with previous dystrophy is similar to what has previously been observed in past surveys. Curiously enough, we have *only rarely* observed the development of a new or recurrent carcinoma in this postoperative dystrophy. I would be interested in knowing what the authors' experience has been.

The authors have not provided us with the actual number of the 106 cases that were involved in determining their excellent but corrected 5 year survival rate of 97.17% or their actual gross 5 year survival rate. Although we know that intercurrent disease is an important factor as a cause of death in patients with cancer of the vulva, I believe that we should report gross 5 year survival rates for each of the clinical stages of the disease, indicating, if you wish, the percent of deaths due to cancer and the percent due to intercurrent disease. Interestingly enough, we have shown via this statistical approach that the percent of deaths due to intercurrent disease in cancer of the vulva increases with the clinical stage of the disease. This observation suggests that there is possibly a significant relationship between the host resistance of a patient to malignancy and the intercurrent disease present in the given patient.

Finally, I heartily endorse the authors' recommendation that radical vulvectomy and bilateral groin dissection be the initial therapy for all Stage I squamous cell carcinomas of the vulva where the stromal invasion is 2 mm or more. And I would add a pelvic node dissection in patients with positive groin nodes or where the primary lesion involves the clitoris.

DR. ALFRED SHERMAN, Detroit, Michigan. I would like to ask the author, particularly in the patients with the 1 to 3 mm invasion in which there is a 3% nodal involvement, about the survival of those patients.

I am quite concerned with a situation where four patients develop inguinal node involvement and also 12% or 13% of patients develop local recurrences. I submit that there is no worse complication for this disease than recurrences in either the groin or in the vulva. So, despite the fact that patients may only have

lesions with 1 to 3 mm of invasion and despite the fact that they may only have a 3% nodal involvement, I think it behooves us to know whether or not nodal dissection in these patients would have increased their survival rate or would have prevented local recurrence even though they only have 3% positive nodes. I do not think that the addition of the inguinal node dissection adds any greater degree of morbidity to the over-all results in these patients and would certainly be justified if it decreased local recurrences or prolonged survival.

DR. PHILIP J. KRUPP, JR., Metairie, Louisiana. This work presents a serious effort to provide more much needed data so that one can individualize the treatment of these patients.

It should be pointed out that there is no definition for microinvasion of the vulva, and, indeed, one may not be able to isolate this entity statistically. I do applaud the authors' attempt to do so.

The sentinel node is a concept which has no basis in fact at this time. No one has yet showed me the location of such a node, and it will take a great deal of information to validate such a concept.

We still need to realize that the basis of therapy for vulvar cancer, as in other cancers, is wide removal of the lesion and its lymph drainage as completely as possible.

DR. MAGRINA (Closing). Dr. Merrill has commented on previous reports by Dr. Wharton and Dr. Parker. The selection of patients in both studies was chiefly based on the size of the lesions and did not take into consideration the clinical status of inguinal nodes, which we did in our series of patients. Although probably small, this could make a difference in the results.

We think that the proposal of DiSaia and colleagues, of sampling the superficial inguinal nodes and then deciding if further lymphadenectomy is indicated, is good for selected patients. However, it does not solve the problem of local recurrence that Dr. Merrill has mentioned. We compared the clinical and histologic factors, referred to previously, with vulvar recurrence and none of the factors showed a significant correlation. The possibility that some of these recurrences may constitute a second primary is raised by the fact that three patients developed a recurrence 10 years or more after the initial therapy.

In relation to our indications for pelvic node dissection, this study covers a 25 year period, and these were patients who were treated at the beginning of the study, when the indications for pelvic lymphadenectomy were still not clear.

We do not have a satisfactory explanation for the difference relative to node involvement between patients with left vulvar lesions and those with right vulvar lesions. The histologic characteristics of the lesions were similar in both groups of patients.

In reply to Dr. Masterson, the type of operative procedure showed no correlation with vulvar recurrence. Also, the margins of excision appeared to be adequate in all surgical specimens. Therefore, we do not know what factors are responsible for local recurrence of the tumor.

You have probably been surprised to see that the 5 year survival rate has been 97%, considering that four of 106 patients died as a result of vulvar cancer. Three of these patients died within 5 years; the fourth patient survived more than 5 years. This is why we have a corrected 5 year survival rate of 97%.

We feel that if treatment or prevention of node metastases is desired in all patients, inguinal lymphadenectomy should be performed with lesions invading the stroma 2 mm or more. However, when we further analyzed our data it was evident that lesions with 3 mm or less of invasion were associated with a low (3%) incidence of node involvement, as compared to almost 20% when the depth of invasion was 4 mm or more. This leaves a place for individualization for inguinal lymphadenectomy in the group of patients with 3 mm or less of invasion, based on the age and condition of the patient and the surgeon's personal approach. Inguinal lymphadenectomy should certainly be included in the initial therapy of patients with 4 mm or more of invasion.

In reply to the floor discussant, among 68 patients with 3 mm or less of invasion only one died as a result of vulvar cancer, as compared to three among 38 patients with 4 mm or more of invasion. However, the difference was not statistically significant.

The nonstress test for the antepartum assessment of fetal reserve

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Seven hundred and twenty-two nonstress tests (NSTs) that were performed on a total of 471 patients were reviewed. The results of the study suggest that the NST is a simple, reliable test as a primary screening procedure in antepartum fetal heart rate (FHR) monitoring. The active and reactive tests were indeed reliable indicators of fetal well-being while the nonreactive test required an additional discriminatory evaluation. A tentative classification is suggested for those cases with FHR decelerations associated with fetal activity and uterine contractions. (AM. J. OBSTET. GYNECOL. 134:460, 1979.)

ACCURATE EVALUATION of fetal well-being and maturity is essential in the management of high-risk pregnancies, which frequently require preterm delivery from an unfavorable or hostile intrauterine environment.

With the fetal heart rate (FHR) monitoring system, evaluation of FHR changes in response to the stress of uterine contractions produced by oxytocin infusion has been employed widely for the assessment of fetal respiratory reserve. The clinical value of the contraction stress test (CST) or the oxytocin challenge test (OCT) has been proved by Pose,[1] Kubli,[2] Ray,[3] and their associates, Freeman,[4] and others[5, 6] in the management of high-risk pregnancies.

More recently, FHR acceleration associated with fetal activity (FA) has received growing attention as a sign of fetal well-being and has been evaluated as a simple test for antepartum assessment of fetal reserve.[7–11] In a previous study,[7] fetal activity acceleration determination (FAD) or the nonstress test (NST) and the CST were performed simultaneously to evaluate the correlation between the two tests. When clear FHR accelerations with vigorous fetal activity were recorded, the subsequent CST was always negative. When inadequate or no FHR acceleration was recorded with infrequent and weak fetal movements (FMs), the subsequent CST was frequently "suspicious" or positive. There was also an excellent correlation between the results of the tests and outcome of the fetuses.

On the basis of this study[7] and with support from others,[8–10] the NST has been used at Henry Ford Hospital since January 1, 1976, as the primary technique for antepartum evaluation of fetal reserve in the management of high-risk pregnancies. The following is a report of our recent clinical evaluation of the NST as a primary screening test in antepartum FHR monitoring.

Material and methods

During a two-year period, from January 1, 1976, to December 31, 1977, the NST was performed 722 times on 471 patients in the fetal monitoring unit of Henry Ford Hospital, Detroit, Michigan, for the evaluation of fetal respiratory reserve. The FHR was recorded by ultrasonogram and abdominal fetal electrocardiogram (FECG) using Corometrics III and IIIA fetal heart rate monitors. Even though fetal activity could be recognized in most cases by abrupt changes on the uterine activity tracing recorded by external tokodynamometer, additional fetal activity markings were recorded by having the patient press the test button or marker on the Corometrics fetal heart rate monitors whenever fetal activity was felt. Table I reveals the reasons for the test.

When more than two FHR accelerations with fetal activity were clearly recorded, it was interpreted that the fetus demonstrated a sign of well-being and was classified as "active" (Fig. 1) FHR acceleration of more than 10 bpm was used as the criterion of the active test.

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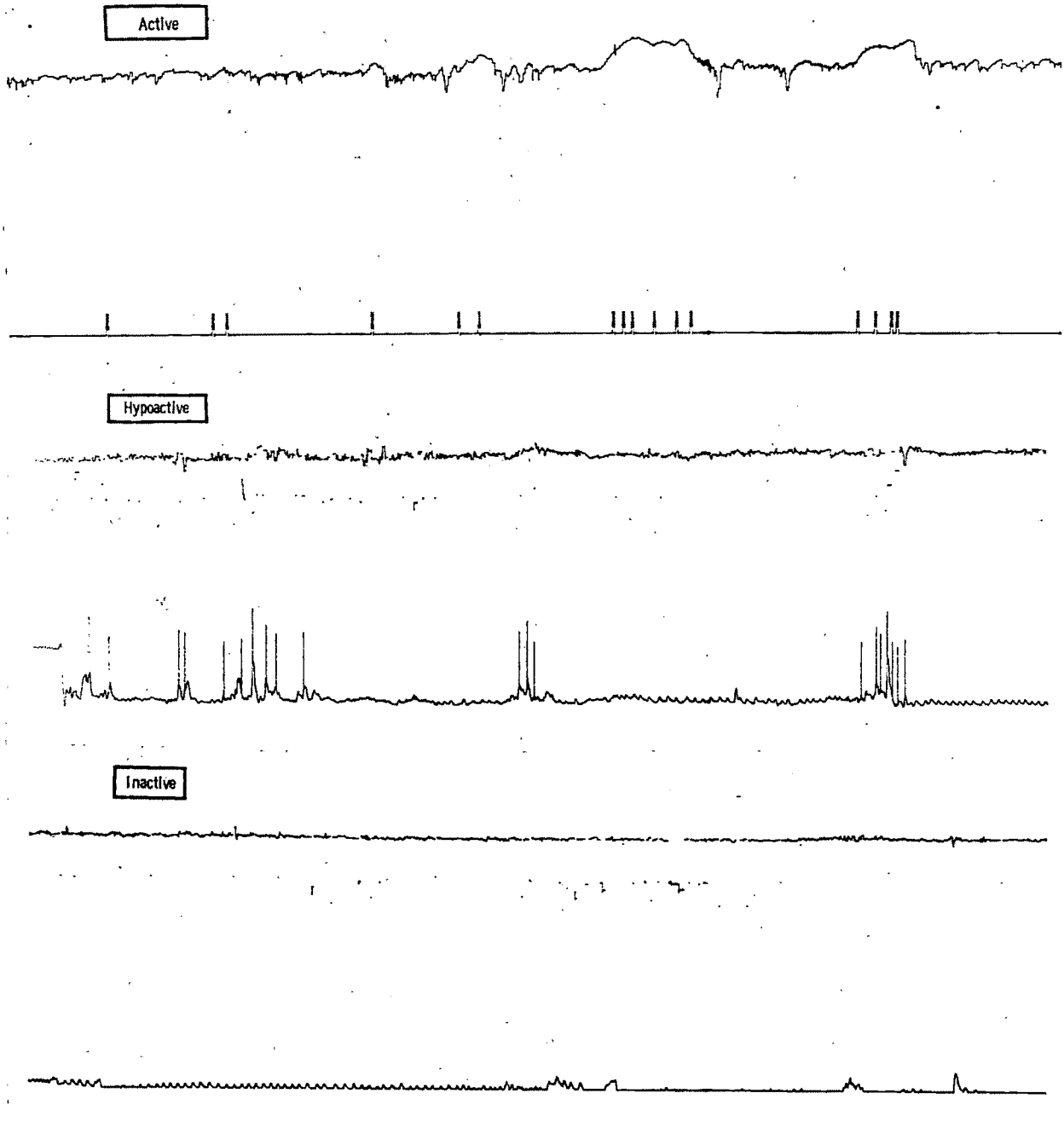


Fig. 1. Examples of active, hypoactive, and inactive NST.

In this group the test was repeated either biweekly or weekly. When the fetus recorded inadequate or questionable FHR accelerations with fetal activity (less than 10 bpm), the test was classified as "hypoactive." An inactive classification was used when the fetus demonstrated no FHR acceleration with infrequent or no fetal activity for the initial 20 minutes of FHR recording. In those cases with hypoactive and inactive tests, external manipulation was applied to stimulate fetal activity. When the fetus recorded FHR accelerations during the extended test with vigorous fetal activity responding to the external stimuli, the test was classified as "reactive." A classification of hypoactive-reactive and inactive-reactive tests was used for these patients and these cases were managed in the same way as were those with the active test. When the fetus did not respond to repeated external stimuli during an extended test, the test was classified as "nonreactive." Only in these nonreactive cases with initial hypoactive and inactive tests was the CST performed for further confirmation of the fetal

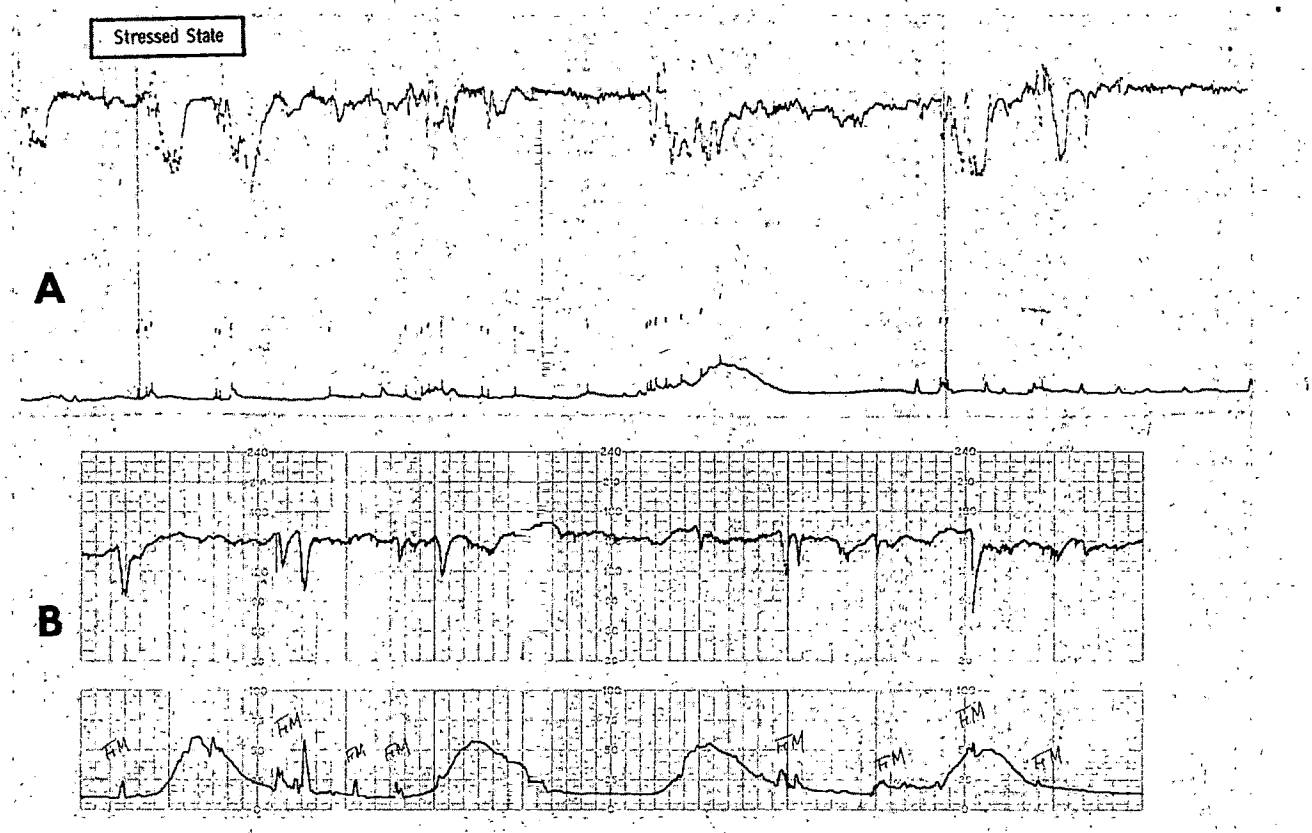


Fig. 2. Examples of a stressed state in NST. *A:* A stressed pattern of variable deceleration associated with fetal activity. Note the acute deceleration and recovery angles with precipitate deceleration and rapid recovery tracings. *B:* A mild degree of variable decelerations with fetal movements continuously observed during the whole process of labor. Note the accelerations associated with uterine contractions.

Table I. Reasons for NST

Reasons for testing	*No.*
Postdate pregnancy	291
Hypertensive disease of pregnancy	176
Diabetes mellitus, Class A to D	73
Chronic hypertension	23
Previous perinatal death	22
Older patients	21
Suspected fetal dysmaturity	16
Decreased fetal activity	14
Rh isoimmunization	12
Uterine bleeding	10
Sickle cell anemia	9
Others	55
Total	722*

*The test was performed on a total of 471 patients.

condition. The CST was performed in a routine manner as described by others.[5, 6]

In several cases, FHR decelerations were recorded continuously with fetal activity and in response to occasional Braxton-Hicks contractions. On the basis of previous observations[12] of the progressive changes in the configuration of variable deceleration and outcome of these cases, a tentative classification for these cases is suggested.

In some cases, 24 hour urinary estriol and human placental lactogen levels were also measured serially along with the tests, although the results of these biochemical analyses were not used for the evaluation of the tests. Management of the patients was based on the clinical impression of each case and the test results. Outcome of each fetus was compared with the results of the tests to evaluate their clinical value.

Results

The NST was performed 722 times on a total of 471 patients. Six hundred and twenty-one tests were active, and 75 tests were reactive (Table II). In these groups all infants were delivered either vaginally or abdominally in good condition (Apgar score 7 or above at 5 minutes) except for three cases. These three infants were moderately depressed (Apgar score 4 to 6 at 5 minutes) with a specific etiology of the low Apgar score. Only one fetus recorded persistent late decelerations during ac-

Table II. Results of 722 NSTs* on 471 patients

Initial test without fetal stimulation	*No.*	*Extended test with fetal stimulation*	*No.*
Active	621		
Hypoactive	82	→ Reactive	75
		→ Nonreactive	7
Inactive	5	→ Nonreactive	5
Stressed	4		
Distressed	2		

*Eight tests were unsatisfactory.

Table III. CST following nonreactive NST

NST	*No.*	*CST*	*No.*
Hypoactive-nonreactive	7	→ Reactive-negative	5
		→ Nonreactive-negative	1
		→ Nonreactive-positive	1
Inactive-nonreactive	5	→ Reactive-negative	2
		→ Nonreactive-positive	3

Table IV. Outcome of the Cases with abnormal NST and CST

NST	*CST*	*No.*	*Apgar score at 5 min.*	*Fetal and neonatal outcome*
Hypoactive-nonreactive	Nonreactive-negative	1	8	Discharged in good condition
Hypoactive-nonreactive	Nonreactive-positive	1	7	Discharged in good condition
Inactive-nonreactive	Nonreactive-positive	3	6,8,8	Two infants were small-for-dates. All were discharged in good condition.
Stressed state		2	8,9*	One infant was small-for-date. Both infants were discharged in good condition
Distressed state		2	3,0*	Neonatal death 3 days after delivery and fetal death 5 days after test

*Delivered vaginally. All other fetuses were delivered abdominally.

tive labor, and it was delivered in good condition by cesarean section (Apgar score 8 at 5 minutes).

Seven hypoactive fetuses were nonreactive to external stimuli. However, five of these recorded definite FHR accelerations with vigorous movements during a subsequent CST for further evaluation of the fetal condition. The CST results were negative in these five infants (Table III), who were delivered vaginally in good condition. In the two remaining hypoactive-nonreactive cases, the subsequent CST was negative in one case but continuously nonreactive. This fetus recorded persistent late decelerations with a mild degree of tachycardia during the induction of labor with intravenous oxytocin infusion on the day following the test. The fetus was delivered by cesarean section in good condition. A subsequent CST was positive in one other case, but the fetus was delivered in good condition by cesarean section on the day of the tests (Table III).

Five inactive FHR recordings were obtained from the five patients with hypertensive disease of pregnancy. Among these patients, two fetuses became reactive during the performance of the subsequent CST, which was negative (Table III). In the three inactive-nonreactive cases, the subsequent CST was positive, and all infants were delivered by cesarean section on the day of the tests. One infant was moderately depressed (Apgar score 6 at 5 minutes), and the other two were delivered in good condition. Signs of intrauterine growth retardation appeared in two infants (Table IV).

A mild degree of variable decelerations with fetal activity and/or uterine contractions was occasionally observed along with FHR accelerations in approximately 15% of the active and reactive tests. However, in four cases FHR decelerations were recorded continuously without a single FHR acceleration. In two fetuses a stressed pattern[12] of variable deceleration with fetal activity and/or uterine contractions was recorded continuously. The configuration of variable deceleration in these cases revealed precipitate deceleration and rapid recovery tracings (Fig. 2, *A*). In this case, when the NST

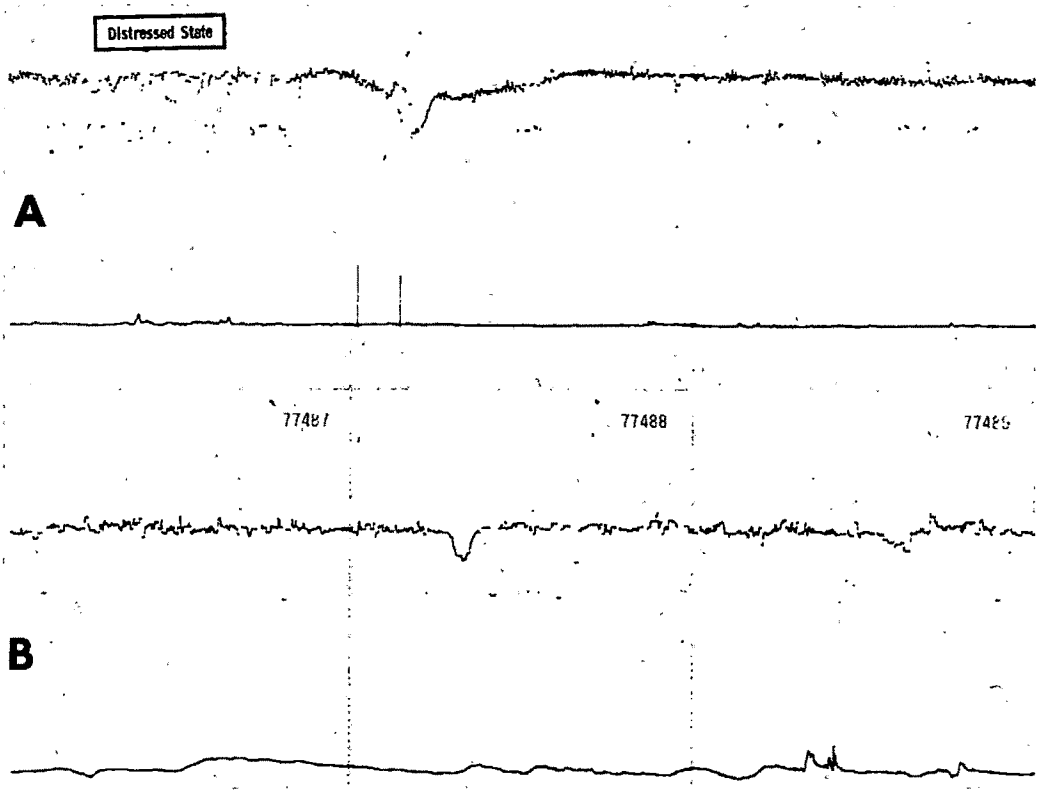


Fig. 3. Examples of a distressed state in a NST. *A:* A recording of what appeared to be a combination of a variable and late deceleration with fetal activity. *B:* Recording in a premature fetus of a distressed pattern of variable decelerations in a NST. Note the smoothly curved deceleration and recovery angles.

was repeated 3 days after the initial test, the fetus again demonstrated a stressed pattern of variable decelerations with fetal activity. Labor was induced with intravenous oxytocin infusion using internal FHR monitoring after the membranes had ruptured. However, after 4 hours of oxytocin infusion the fetus was delivered by cesarean section because of recurrent variable decelerations and poor progress of labor. A male infant, weighing 3,098 grams, was delivered in good condition (Table IV). The umbilical cord was wrapped around the neck, left shoulder, and left forearm. One other fetus who demonstrated a stressed pattern of variable decelerations with fetal activity in both the initial and repeated tests was delivered vaginally in good condition (Apgar score 9 at 5 minutes) (Table IV). Fetal activity continuously produced a mild degree of variable deceleration during the entire labor (Fig. 2, *B*).

A fetus of a postdate pregnancy demonstrated what appeared to be a combination of the distressed pattern of variable and late decelerations during the NST (Fig. 3, *A*). Although the patient was inadvertently released, she was admitted to the hospital in labor one week later with a history of no fetal movements for 2 days. The patient was delivered of a macerated female infant weighing 3,200 grams (Table IV). A fetus of 30 weeks of gestation recorded variable decelerations with somewhat blunted decelerations and recovery angles during a NST (Fig. 3, *B*). The mother was hospitalized with pregnancy-aggravated hypertension. On the evening of the test day, the patient started premature labor after the membranes had ruptured. The fetus demonstrated the distressed pattern of variable decelerations[12] during labor (Fig. 4) and was delivered by cesarean section in a severely depressed condition (Apgar score 3 at 5 minutes), and died of pneumonitis and septicemia on the third day of extrauterine life (Table IV).

In one case, what appeared to be a sinusoidal pattern[8, 16] was recorded for 12 minutes during the initial NST. The sinusoidal pattern disappeared spontaneously and the fetus recorded accelerations with FMs on the normal baseline FHR (Fig. 5). This FHR pattern was not observed when the test was repeated 3 days later, and the NST was active. The fetus did not dem-

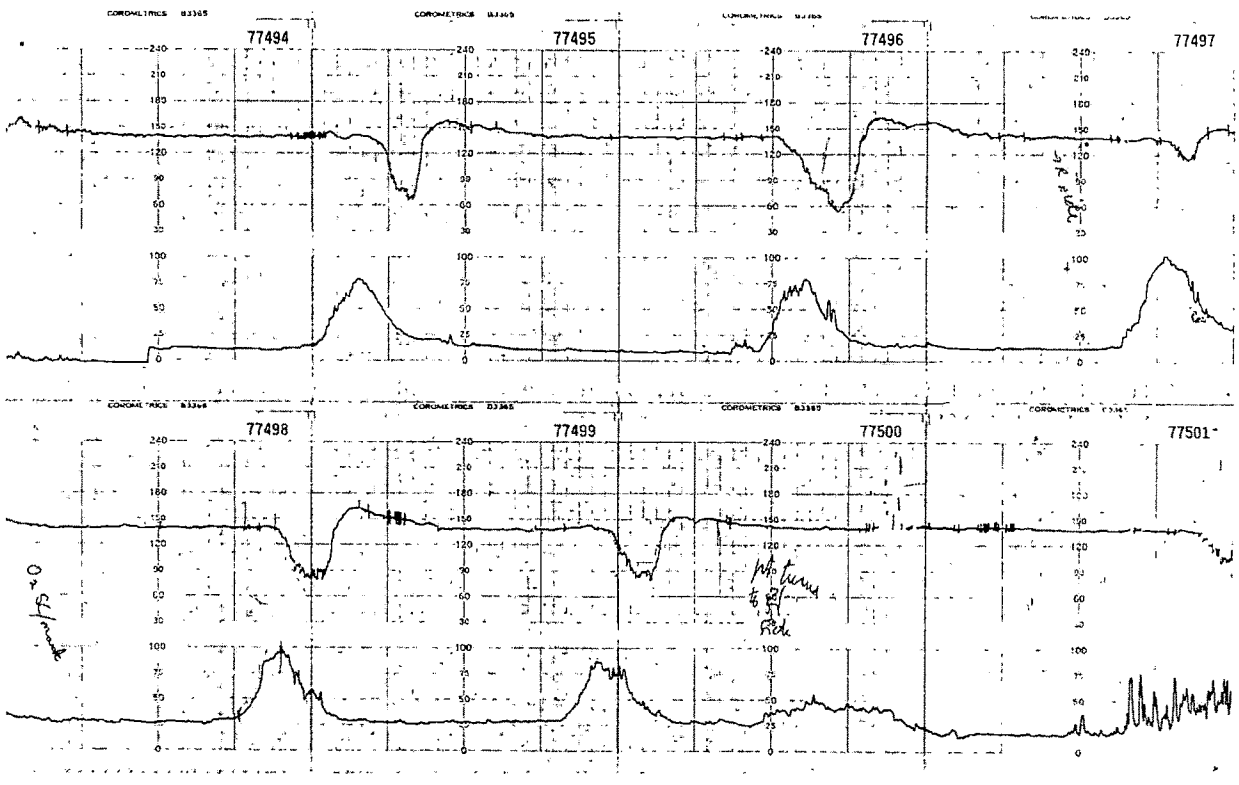


Fig. 4. A distressed pattern of variable decelerations in labor. Note the smoothly curved deceleration and recovery angles with overshoot acceleration.

onstrate a sinusoidal FHR pattern during labor and was delivered vaginally in good condition 8 days after the initial NST.

In seven instances the initial NST was unsatisfactory. However, in four cases the repeated NST was satisfactory and active. In two other cases, the patients went into labor spontaneously before the performance of a repeat test and were delivered of their infants in good condition. In one case, a repeated NST was again unsatisfactory because of extreme obesity and hydramnios. This patient was evaluated with biochemical tests.

Comment

The results of the study suggest that the NST is a simple, reliable test for primary screening in antepartum FHR monitoring. The active and reactive NSTs were indeed reliable indicators of fetal well-being. No fetal death occurred in these cases, and with three exceptions all fetuses in this group were delivered in good condition (Apgar score 7 and over at 5 minutes). These three cases all had a specific etiology of the fetal depression.

It was again apparent that the nonreactive NST with an initial hypoactive or inactive test requires additional discriminatory evaluation. For this purpose, the CST was used. Five cases with a hypoactive-nonreactive NST and two cases with an inactive-nonreactive NST became reactive to the stress of uterine contractions during the subsequent CST for further evaluation of the fetal condition (Table III). Phenobarbital administered to the patients with hypertensive disease of pregnancy might be the cause of the nonreactive test in some cases in this group.

Manning[13] suggested the need for further discriminatory evaluation of fetuses who had nonreactive-positive CSTs subsequent to nonreactive NSTs, with the observation of fetal breathing movements through real-time ultrasound. In his series, there was a much higher incidence of intrauterine growth retardation and low Apgar scores among the fetuses which revealed no breathing movements with the positive CST. The ideal test in antepartum fetal monitoring should not yield false positive signs of fetal compromise. At the same time, the test should give an early warning of fetal compromise and allow us to prevent fetal depression.

Recently, Braly and Freeman[14] evaluated the significance of baseline reactivity in their positive OCT cases. The fetal outcome was uniformly good in those cases with baseline FHR reactivity. Half of these pa-

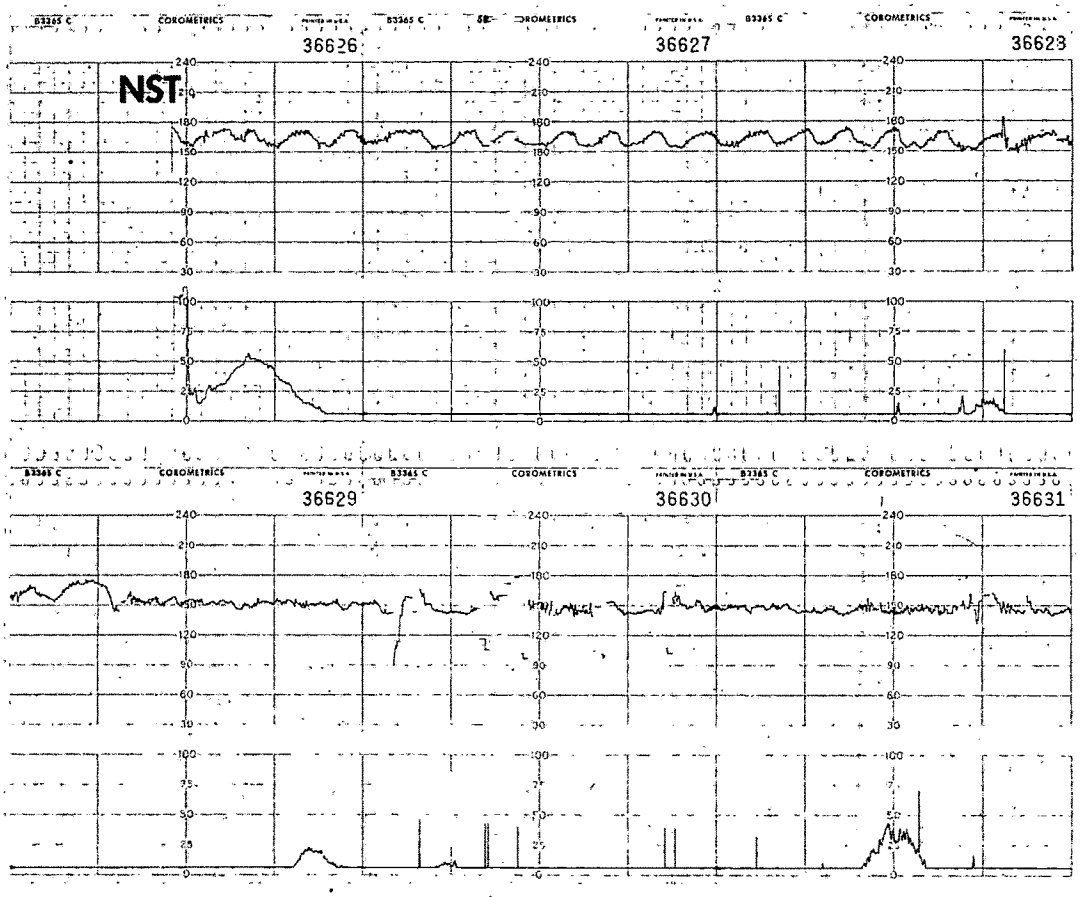


Fig. 5. Recording of what appeared to be a sinusoidal FHR pattern for 12 minutes. Note the spontaneous disappearance of the sinusoidal pattern.

tients tolerated labor well, without revealing signs of fetal distress, and were delivered vaginally of their infants. When the positive OCT was associated with a nonreactive FHR recording, a trial of labor uniformly resulted in signs of fetal distress. It is apparent, in this study, that FHR reactivity was present in all cases with a false positive OCT. This study also suggests that a nonreactive-positive CST is a reliable indicator of fetal compromise. However, a further discriminatory evaluation with fetal breathing movements may be helpful in extreme prematurity with a nonreactive-positive CST.

Rochard and associates[8] and others[9-11] classified the NST into two main groups—"reactive" and "nonreactive" tests. The NST was classified as "active," "hyporeactive," and "inactive" in this study, depending on the degree of FHR accelerations associated with fetal activity. When the external stimuli or stress of uterine contractions was applied to the fetus, then a reactive or nonreactive classification is appropriate, depending on the fetal response to the stimuli or stresses (Fig. 5).

Occasionally FHR decelerations were observed between the accelerations in approximately 15% of active and reactive NSTs. Visser and Huisjes[10] classified this group as "decelerative." In their series, 13 of the 20 patients with a decelerative NST showed signs of fetal distress in labor. In 12 of the 20 patients with a decelerative test, the infants were small for dates. In the present study, however, all the active and reactive tests that were recorded with occasional FHR decelerations resulted in delivery of infants in good condition. An increased incidence of intrauterine growth retardation was not observed in this group of patients.

Using a high paper speed in FHR monitoring, Timor-Tritsch and associates[15] observed that 66.7% of fetal activity produced a combination of FHR accelerations and after-coming decelerations. In four cases in our series, however, the fetus demonstrated FHR decelerations continuously with fetal activity and uterine contractions without a single recording of FHR acceleration. Even though the number is limited to four cases, it was apparent in this study that these cases were composed of two different groups of fetuses. Two fetuses that demonstrated a stressed pattern of variable

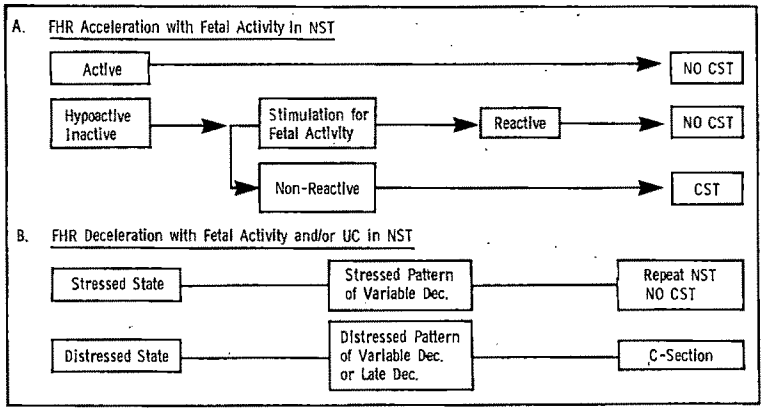


Fig. 6. Evaluation of fetal well-being using FHR monitor. *DEC:* Deceleration; *UC:* uterine contraction.

deceleration[12] during the performance of the NST were delivered in good condition, while the other two who demonstrated a distressed pattern of variable deceleration[12] and a combination of distressed variable and late decelerations resulted in prenatal deaths.

On the basis of the clinical experience with these cases, a tentative classification is suggested for the deceleration group in Fig. 6. Admittedly, more clinical studies are needed for better evaluation of fetal status in this deceleration group. An abdominal wall FECG enables us to evaluate FHR beat-to-beat variability and will be helpful in the differentiation of the stressed and distressed fetus in the deceleration group.

In the series reported by Kubli and associates,[16] a sinusoidal FHR pattern was found in nine of 12 fetuses prior to death. Rochard and co-workers[8] observed 10 perinatal deaths among the 20 fetuses demonstrating a sinusoidal FHR pattern. An additional 40% of fetuses with this type of FHR pattern in their series required prolonged hospitalization after birth. In one case observed in our series, the recording of a sinusoidal FHR pattern was temporary and was not found during the repeated NST or in labor.

In summary, the NST is a simple, reliable test as a primary screening procedure in antepartum fetal monitoring. The active and reactive tests were indeed reliable indicators of fetal well-being, while nonreactive tests were needed for further discriminatory evaluation. A tentative classification is suggested for those cases with FHR decelerations associated with fetal activity and uterine contractions. Since the NST requires only 20 to 30 minutes of FHR recording without oxytocin infusion, it is suitable as an office procedure.

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Discussion

DR. RICHARD P. BENDEL, Minneapolis, Minnesota. This paper by Lee and Drukker adds to the growing list of reports indicating that the NST is a valuable tool in the antepartum assessment of fetal-placental reserve. At Hennepin County Medical Center, I have reviewed nearly 500 NSTs done during the past two years and have found nearly identical results, i.e., an active fetus with good FHR accelerations is virtually assured of a good outcome. Obviously, a normal NST does not preclude a poor fetal outcome if labor is mismanaged, cephalopelvic disproportion is not recognized, or a catastrophic event such as abruptio placentae supervenes.

When the fetus is hypoactive or inactive, the authors proceed to stimulate the fetus, and if it then becomes reactive, that also is reassuring and the fetus can be considered with those fetuses active to begin with. We likewise have resorted to stimulation of the fetus by external manipulation or having the mother get up and move around for a few minutes and then reapplying the monitor. Up until now I have been questioning whether that ploy was legitimate. I am glad to learn that these hypoactive-reactive fetuses are also healthy.

Using an acceleration of 10 bpm as the criterion for an active test is disturbing to me. Initially, we used an acceleration of 20 bpm as the end point, but we soon realized that an acceleration of 15 bpm was equally predictive of good fetal reserve. However, I have found some records where apparent accelerations of 10 bpm were associated with a positive contraction stress test (CST) and decreased uteroplacental reserve. This is especially a problem with ultrasound pickup of the FHR, where the apparent baseline variability can often be 10 bpm. I would like Dr. Lee to comment on this point.

Last, I find very confusing the discussion of the four cases where the fetus showed no accelerations and continuous variable deceleration with fetal activity and/or uterine contractions. The authors classified these into two categories called "stressed" and "distressed" patterns. The criteria for these patterns are apparently discussed in an unpublished work. Without presenting further explanatory material in the text of this paper, it is almost impossible to understand their classification as set out in Fig. 6.

DR. R. W. TAYLOR, London, England. Dr. Lee's previous paper in 1976 led me to use the NST in the study of high-risk patients in my own department.

I find the philosophy behind the NST satisfying. It is an attempt to determine the well-being of the fetus, where all placental function tests so far described tell of one aspect of function of that organ and can at times be seriously misleading.

The OCT meets the requirements of a test of fetal well-being but probably because of early poor results before the days of second electronic fetal monitoring this has not found wide acceptance in Britain. Perhaps the very term "stress test" had something to do with that rejection.

We have only 2 years' completed experience but it does seem to confirm the conclusions presented. The main problem with this paper is in the definition of a "high-risk" case. This is so wide that the number of "sick" fetuses is very small. In this the authors are doing what they set out to do, namely, evaluate the NST as a primary test, but it would stand better if there were more positive results to analyze.

In our unit we have used the NST mainly where there is other evidence of fetal malaise—poor growth rate, maternal hypertension, poor liquor volume, or poor urinary excretion of estriol and pregnanediol.

In 73 patients monitored for a mean period of 11.7 days between 33 and 37 weeks, 17 patients showed good signs of fetal activity and good fetal heart acceleration. All were subsequently delivered of babies of good weight, in good condition, and we concluded that our initial diagnosis was incorrect and our fears groundless.

In 56 babies where we had a poor response on at least two occasions labor was induced. In the past 18 months our usual method of delivery has included the insertion overnight of prostaglandin paste, with subsequent artificial rupture of membranes and oxytocin infusion if necessary. There were 14 vaginal deliveries and 22 babies were delivered by cesarean section—18 because of fetal distress, usually confirmed by a fetal scalp sample. In 20 cases where placental function tests were poor but the NST was initially satisfactory, there was a mean gain of 17 days in utero before the NST became poor and we felt obliged to deliver the baby. In our view this fact alone justifies the faith that the authors would have us put in this test. At present the NST is often difficult to interpret and only for a moderately sophisticated unit. However, with the availability of computer-assisted monitoring this should change.

DR. PETER E. FEHR, Minneapolis, Minnesota. Many people have shown that there is a sleep cycle in the fetus and mothers have said, "I think the baby has been

sleeping for a bit." I think it is important for us to realize that a normal fetal sleep cycle can run probably 20 minutes, so we might be inclined to call a 30 minute test "positive" unless we do some stimulation.

Sureau and colleagues[1] of Paris, France, would certainly disagree with your statement on the sinusoidal test, and though I have heard Sureau and I have heard you, I am going to be doing contraction stress testing on all sinusoidal patterns because I am concerned when I see a pattern that is internationally considered dangerous.

My own feeling is you are overreacting to a positive CST by doing a cesarean section on the day of the test. I believe that the statistics will show that almost 50% of these babies can be delivered vaginally, and because of the false positive CST rate, I believe that an attempted induction of labor with good electronic monitoring and scalp sampling is an appropriate approach. I would challenge anyone in our hospital who would perform a cesarean section on the basis of a positive CST without an attempted induction of labor.

Finally, I believe that the NST carefully applied at weekly intervals to patients who have a potentially diminished fetal-placental reserve is a very valid test and certainly should reduce significantly the stillbirth rate of unknown etiology in that high-risk group.

I would certainly agree with the idea of using the CST in cases where the NST is doubtful, and as far as the second category or the two new categories, Dr. Bendel and I concur that we have some real question about their validity.

In our own series, when a patient is having spontaneous contractions and there are late decelerations in the fetus, we assume this is a positive stress test, and we regard these to be the same as any other late decelerations in labor. If the patient has a closed cervix and three contractions in 10 minutes, all of them accompanied by late decelerations, the patient should probably be delivered by cesarean section.

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DR. JACQUES F. ROUX, Lansing, Michigan. Dr. Lee was one of the first investigators to outline in the literature the importance of fetal motions as they relate to the FHR. This was a very valuable contribution to our field.

However, we should remain critical of the NST because no data were obtained in patients who were not stress-tested.

It would have been an excellent contribution to our understanding of the NST if the author had chosen at random patients who would be stress-tested but who would be managed without consideration of the results of the NST. It would be a study very similar to that of Dr. Haverkamp. His group has questioned with reason the clinical value of FHR monitoring in well-supervised patients.

In our experience, an abnormal NST was associated two thirds of the time with a problem during labor, but it could be a minor problem, for instance, a loose cord around the neck, an abnormal presentation such as a posterior presentation, or a near-term breech presentation.

In most of the cases cesarean section was not performed. On the other hand, a normal stress test was associated with complications during labor 25% of the time. I believe that the NST is a useful test if it is evaluated in the general clinical context of the case. The NST should replace the OCT because it can be repeated more frequently, it is less emotionally "loaded," and it is almost as good a predictor of fetal outcome as the OCT.

DR. ROGER HERTZ, Cleveland, Ohio. I would like to bring up one point regarding fetal behavioral cycling based on work done in Dr. Rosen's laboratories at Cleveland Metropolitan General Hospital by Timor-Tritsch and associates.[1]

In a research setting, we have noted that "quiet" periods or what we think may be a fetal "quiet sleep state" does indeed occur and that these periods may be considerably longer than previously appreciated.

In a study of 16 normal term pregnant patients in our laboratories fetal "quiet sleep" or periods of inactivity with minimal variation in FHR have been observed for up to 50 minutes. The finding that normal fetuses can have prolonged inactive periods should be borne in mind in analyzing antepartum monitoring data. Interrupting these periods of inactivity by stimulation (evoked response) as suggested by others may be a reasonable approach requiring further study.

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DR. ROBERT A. MUNSICK, Indianapolis, Indiana. I would like to ask Dr. Lee if he can review his data and tell us the possible difference in results if one looked only at the presence of fetal motion on the tokograph without checking the heart rate. Does he have data as to the results of only palpation of motion? Would this have the same results as a history taken from the mother regarding activity in the previous 24 hours?

DR. LEE (Closing). I am encouraged by the comments made by Professor Taylor since their experience in England is similar to ours. In the previous studies,[1, 2] the term "fetal activity acceleration determination" was used on the basis of the following concept: If a fetus

can perform a vigorous activity which requires FHR acceleration, the fetus can be considered to have a good functional reserve. A chronically decreased fetal reserve may make the fetus unable to perform a vigorous activity which requires FHR acceleration.

I am also encouraged by the discussion from Dr. Roux since he has recognized our previous study[1] as a first paper that appeared in a journal.

Dr. Roux and Professor Taylor questioned the justification of the cesarean section in the case of a nonreactive-positive CST following a nonreactive NST. Recently Braly and Freeman[3] evaluated the significance of baseline FHR reactivity in their positive OCT cases. When the positive OCT was associated with a nonreactive baseline FHR recording, a trial of labor uniformly resulted in signs of fetal distress. Our previous experience was similar to the results of this study, and because of this reason we have included baseline FHR reactivity in the interpretation of the CST.

In the classification of an active test, we used a clear recording of more than two FHR accelerations associated with activity. I think that the presence of recognizable FHR accelerations is more important than the number of beats of acceleration per minute. Usually, FHR acceleration of more than 10 bpm can be recognized as a clear FHR acceleration. By using more than two FHR accelerations over 10 bpm as the minimum criterion of an active test we could eliminate many hypoactive and nonreactive NSTs.

There was a question regarding the necessity for and method of fetal stimulation to produce fetal activity. We all have observed that each fetus demonstrates its own cycle of quiet and active periods. The duration of each cycle is variable, especially in the fetus of a high-risk pregnancy. External stimulation has been effective in the differentiation of the healthy fetus in a quiet state from the one who has a low functional reserve. Administration of phenobarbital has been used in the management of patients with hypertensive disease of pregnancy. External stimulation is especially necessary in these cases. We have used external shaking of the fetus as a method of stimulation since it has been used effectively and safely. In certain cases, uterine contractions were necessary to awaken the fetus from the quiet sleep state.

Using a high-speed recording, Timor-Tritsch and associates[4] demonstrated that 99.7% of fetal movement lasting more than 3 seconds was actually associated with FHR accelerations. A question raised was whether the fetal activity recording alone is sufficient as a test. We would like to evaluate both FHR accelerations and fetal activity as a test, since in certain cases fetal activity produced FHR decelerations.

European investigators, including Kubli and Rochard and their associates, have observed more frequently the sinusoidal FHR in a compromised fetus. We observed only one case of what appeared to be a sinusoidal FHR for only 12 minutes and this FHR pattern was not observed in the repeated test or in labor. Because of a limited, rather confusing experience with the sinusoidal FHR, we could not include this FHR in our classification of NST at the present time.

A further explanation was requested on the classification of the NST shown in Fig. 6. When the NST is active or reactive, it is not necessary to proceed to the CST. However, a nonreactive NST with an initial hypoactive or inactive test does require the performance of a CST for further confirmation of the fetal condition. Five fetuses with a hypoactive-nonreactive test and two fetuses with an inactive-nonreactive test became reactive during the performance of the CST and all CSTs were negative. Two fetuses demonstrated a stressed pattern of variable deceleration[5] without revealing a single FHR acceleration during the NST. The configuration of variable deceleration in these cases revealed an acute deceleration and recovery angle with precipitate deceleration and rapid recovery tracings.

A blunting or rounding of deceleration and recovery angles and a smoothing of the rectangular waveform with loss of jaggedness are progressive changes observed in the distressed pattern of variable deceleration.[5] These changes may represent a sluggish reaction of the autonomic nervous system in the hypoxic or acidotic fetus to hemodynamic changes occurring during umbilical cord compression.

Two fetuses who displayed a stressed pattern of variable deceleration were delivered in good condition. If the fetus is premature, the NST can be repeated. However, the CST is not recommended since uterine contractions may place more stress on the fetus. Perinatal death occurred in one fetus who demonstrated a distressed pattern of variable deceleration and in one who displayed what appeared to be a combination of a distressed pattern of variable deceleration and uniform deceleration. Admittedly, more study is needed in this deceleration group. Nevertheless, a tentative classification was suggested since these cases were composed of two different groups of fetuses.

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  the patient with moderate to severe vasomotor symptoms with no contraindications to estrogen therapy.
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- ESTABLISH THE CYCLE OF TREATMENT
  be sure the patient understands the need for an interrupted regimen: a "rest period" each month when *no* estrogen is taken.
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Please see Brief Summary of Prescribing Information on the last page.

BRIEF SUMMARY
(FOR FULL PRESCRIBING INFORMATION AND PATIENT INFORMATION, SEE PACKAGE CIRCULAR)
PREMARIN® Brand of Conjugated Estrogens Tablets, U.S.P.

1. ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA.

Three independent case control studies have reported an increased risk of endometrial cancer in postmenopausal women exposed to exogenous estrogens for more than one year.[1-3] This risk was independent of the other known risk factors for endometrial cancer. These studies are further supported by the finding that incidence rates of endometrial cancer have increased sharply since 1969 in eight different areas of the United States with population-based cancer reporting systems, an increase which may be related to the rapidly expanding use of estrogens during the last decade.[4] The three case control studies reported that the risk of endometrial cancer in estrogen users was about 4.5 to 13.9 times greater than in nonusers. The risk appears to depend on both duration of treatment[1] and on estrogen dose.[3] In view of these findings, when estrogens are used for the treatment of menopausal symptoms, the lowest dose that will control symptoms should be utilized and medication should be discontinued as soon as possible. When prolonged treatment is medically indicated, the patient should be reassessed on at least a semiannual basis to determine the need for continued therapy. Although the evidence must be considered preliminary, one study suggests that cyclic administration of low doses of estrogen may carry less risk than continuous administration;[3] it therefore appears prudent to utilize such a regimen. Close clinical surveillance of all women taking estrogens is important. In all cases of undiagnosed persistent or recurring abnormal vaginal bleeding, adequate diagnostic measures should be undertaken to rule out malignancy. There is no evidence at present that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic doses.

2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY.

The use of female sex hormones, both estrogens and progestogens, during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a non-steroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare.[5,6] This risk has been estimated as not greater than 4 per 1000 exposures.[7] Furthermore, a high percentage of such exposed women (from 30 to 90 percent) have been found to have vaginal adenosis,[8-12] epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether they are precursors of malignancy. Although similar data are not available with the use of other estrogens, it cannot be presumed they would not induce similar changes. Several reports suggest an association between intrauterine exposure to female sex hormones and congenital anomalies, including congenital heart defects and limb reduction defects.[13-16] One case control study[16] estimated a 4.7-fold increased risk of limb reduction defects in infants exposed in utero to sex hormones (oral contraceptives, hormone withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some of these exposures were very short and involved only a few days of treatment. The data suggest that the risk of limb reduction defects in exposed fetuses is somewhat less than 1 per 1000. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well controlled studies that progestogens are effective for these uses. If PREMARIN is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the advisability of pregnancy continuation.

DESCRIPTION: PREMARIN (Conjugated Estrogens Tablets, U.S.P.) for oral administration contains a mixture of estrogens, obtained exclusively from natural sources, blended to represent the average composition of material derived from pregnant mares' urine. It contains estrone, equilin, and 17α-dihydroequilin, together with smaller amounts of 17α-estradiol, equilenin, and 17α-dihydroequilenin as salts of their sulfate esters.

INDICATIONS: Based on a review of PREMARIN Tablets by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications for use as follows:

Effective:

1. Moderate to severe *vasomotor* symptoms associated with the menopause. (There is no evidence that estrogens are effective for nervous symptoms or depression without associated vasomotor symptoms, and they should not be used to treat such conditions.)
2. Atrophic vaginitis.
3. Kraurosis vulvae.
4. Female hypogonadism.
5. Female castration.
6. Primary ovarian failure.
7. Breast cancer (for palliation only) in appropriately selected women and men with metastatic disease.
8. Prostatic carcinoma—palliative therapy of advanced disease.
9. Postpartum breast engorgement—Although estrogens have been widely used for the prevention of postpartum breast engorgement, controlled studies have demonstrated that the incidence of significant painful engorgement in patients not receiving such hormonal therapy is low and usually responsive to appropriate analgesic or other supportive therapy. Consequently, the benefit to be derived from estrogen therapy for this indication must be carefully weighed against the potential increased risk of puerperal thromboembolism associated with the use of large doses of estrogens.[19]

PREMARIN HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING).

"Probably" effective: For estrogen deficiency-induced osteoporosis, and only when used in conjunction with other important therapeutic measures such as diet, calcium, physiotherapy, and good general health-promoting measures. Final classification of this indication requires further investigation.

CONTRAINDICATIONS: Estrogens should not be used in women (or men) with any of the following conditions: 1. Known or suspected cancer of the breast except in appropriately selected patients being treated for metastatic disease. 2. Known or suspected estrogen-dependent neoplasia. 3. Known or suspected pregnancy. (See Boxed Warning). 4. Undiagnosed abnormal genital bleeding. 5. Active thrombophlebitis or thromboembolic disorders. 6. A past history of thrombophlebitis, thrombosis, or thromboembolic disorders associated with previous estrogen use (except when used in treatment of breast or prostatic malignancy).

WARNINGS: At the present time there is no satisfactory evidence that estrogens given to postmenopausal women increase the risk of cancer of the breast,[17] although a recent study has raised this possibility.[18] There is a need for caution in prescribing estrogens for women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms. A recent study has reported a 2- to 3-fold increase in the risk of surgically confirmed gallbladder disease in women receiving postmenopausal estrogens.[17]

Adverse effects of oral contraceptives may be expected at the larger doses of estrogen used to treat prostatic or breast cancer or postpartum breast engorgement; it has been shown that there is an increased risk of thrombosis in men receiving estrogens for prostatic cancer and women for postpartum breast engorgement.[19-22] Users of oral contraceptives have an increased risk of diseases, such as thrombophlebitis, pulmonary embolism, stroke, and myocardial infarction.[23-30] Cases of retinal thrombosis, mesenteric thrombosis, and optic neuritis have been reported in oral contraceptive users.[31,32] An increased risk of postsurgery thromboembolic complications has also been reported in users of oral contraceptives.[33,34] If feasible, estrogen should be discontinued at least 4 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization. Estrogens should not be used in persons with active thrombophlebitis, thromboembolic disorders, or in persons with a history of such disorders in association with estrogen use. They should be used with caution in patients with cerebral vascular or coronary artery disease. Large doses (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown[35] to increase the risk of nonfatal myocardial infarction, pulmonary embolism and thrombophlebitis. When doses of this size are used, any of the thromboembolic and thrombotic adverse effects should be considered a clear risk.

Benign hepatic adenomas should be considered in estrogen users having abdominal pain and tenderness, abdominal mass, or hypovolemic shock. Hepatocellular carcinoma has been reported in women taking estrogen-containing oral contraceptives.[36] Increased blood pressure may occur with use of estrogens in the menopause[37] and blood pressure should be monitored with estrogen use. A worsening of glucose tolerance has been observed in patients on estrogen-containing oral contraceptives. For this reason, diabetic patients should be carefully observed. Estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases.

PRECAUTIONS: Physical examination and a complete medical and family history should be taken prior to the initiation of any estrogen therapy with special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolau smear. As a general rule, estrogen should not be prescribed for longer than one year without another physical examination being performed. Conditions influenced by fluid retention such as asthma, epilepsy, migraine, and cardiac or renal dysfunction, require careful observation. Certain patients may develop manifestations of excessive estrogenic stimulation, such as abnormal or excessive uterine bleeding, mastodynia, etc. Oral contraceptives appear to be associated with an increased incidence of mental depression.[23a] Patients with a history of depression should be carefully observed. Preexisting uterine leiomyomata may increase in size during estrogen use. The pathologist should be advised of estrogen therapy when relevant specimens are submitted. If jaundice develops in any patient receiving estrogen, the medication should be discontinued while the cause is investigated. Estrogens should be used with care in patients with impaired liver function, renal insufficiency, metabolic bone diseases associated with hypercalcemia, or in young patients in whom bone growth is not complete.

The following changes may be expected with larger doses of estrogen:

a. Increased sulfobromophthalein retention.

b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.

c. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by PBI, T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered.

d. Impaired glucose tolerance.

e. Decreased pregnanediol excretion.

f. Reduced response to metyrapone test.

g. Reduced serum folate concentration.

h. Increased serum triglyceride and phospholipid concentration.

As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk.

ADVERSE REACTIONS: The following have been reported with estrogenic therapy, including oral contraceptives: breakthrough bleeding, spotting, change in menstrual flow; dysmenorrhea; premenstrual-like syndrome, amenorrhea during and after treatment; increase in size of uterine fibromyomata; vaginal candidiasis, change in cervical erosion and in degree of cervical secretion; cystitis-like syndrome; tenderness, enlargement, secretion (of breasts); nausea, vomiting; abdominal cramps, bloating; cholestatic jaundice; chloasma or melasma which may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair, hirsutism; steepening of corneal curvature; intolerance to contact lenses; headache, migraine, dizziness, mental depression, chorea; increase or decrease in weight; reduced carbohydrate tolerance, aggravation of porphyria; edema; changes in libido.

ACUTE OVERDOSAGE: May cause nausea, and withdrawal bleeding may occur in females.

DOSAGE AND ADMINISTRATION: 1. *Given cyclically for short term use only:* For treatment of moderate to severe *vasomotor* symptoms, atrophic vaginitis, or kraurosis vulvae associated with the menopause (0.3 to 1.25 mg or more daily).

The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible.

Administration should be cyclic (e.g., three weeks on and one week off).

Attempts to discontinue or taper medication should be made at three to six month intervals.

2. *Given cyclically:* Female hypogonadism. Female castration. Primary ovarian failure. Osteoporosis.

Female hypogonadism—2.5 to 7.5 mg daily, in divided doses for 20 days, followed by a rest period of 10 days' duration. If bleeding does not occur by the end of this period, the same dosage schedule is repeated. The number of courses of estrogen therapy necessary to produce bleeding may vary depending on the responsiveness of the endometrium.

If bleeding occurs before the end of the 10 day period, begin a 20 day estrogen-progestin cyclic regimen with PREMARIN (Conjugated Estrogens Tablets, U.S.P.), 2.5 to 7.5 mg daily in divided doses, for 20 days. During the last five days of estrogen therapy, give an oral progestin. If bleeding occurs before this regimen is concluded, therapy is discontinued and may be resumed on the fifth day of bleeding.

Female castration and primary ovarian failure—1.25 mg daily, cyclically. Adjust upward or downward according to response of the patient. For maintenance, adjust dosage to lowest level that will provide effective control.

Osteoporosis (to retard progression)—1.25 mg daily, cyclically.

3. *Given for a few days:* Prevention of postpartum breast engorgement—3.75 mg every four hours for five doses, or 1.25 mg every four hours for five days.

4. *Given chronically:* Inoperable progressing prostatic cancer—1.25 to 2.5 mg three times daily.

Inoperable progressing breast cancer in appropriately selected men and postmenopausal women—10 mg three times daily for a period of at least three months.

Patients with an intact uterus should be monitored for signs of endometrial cancer and appropriate measures taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

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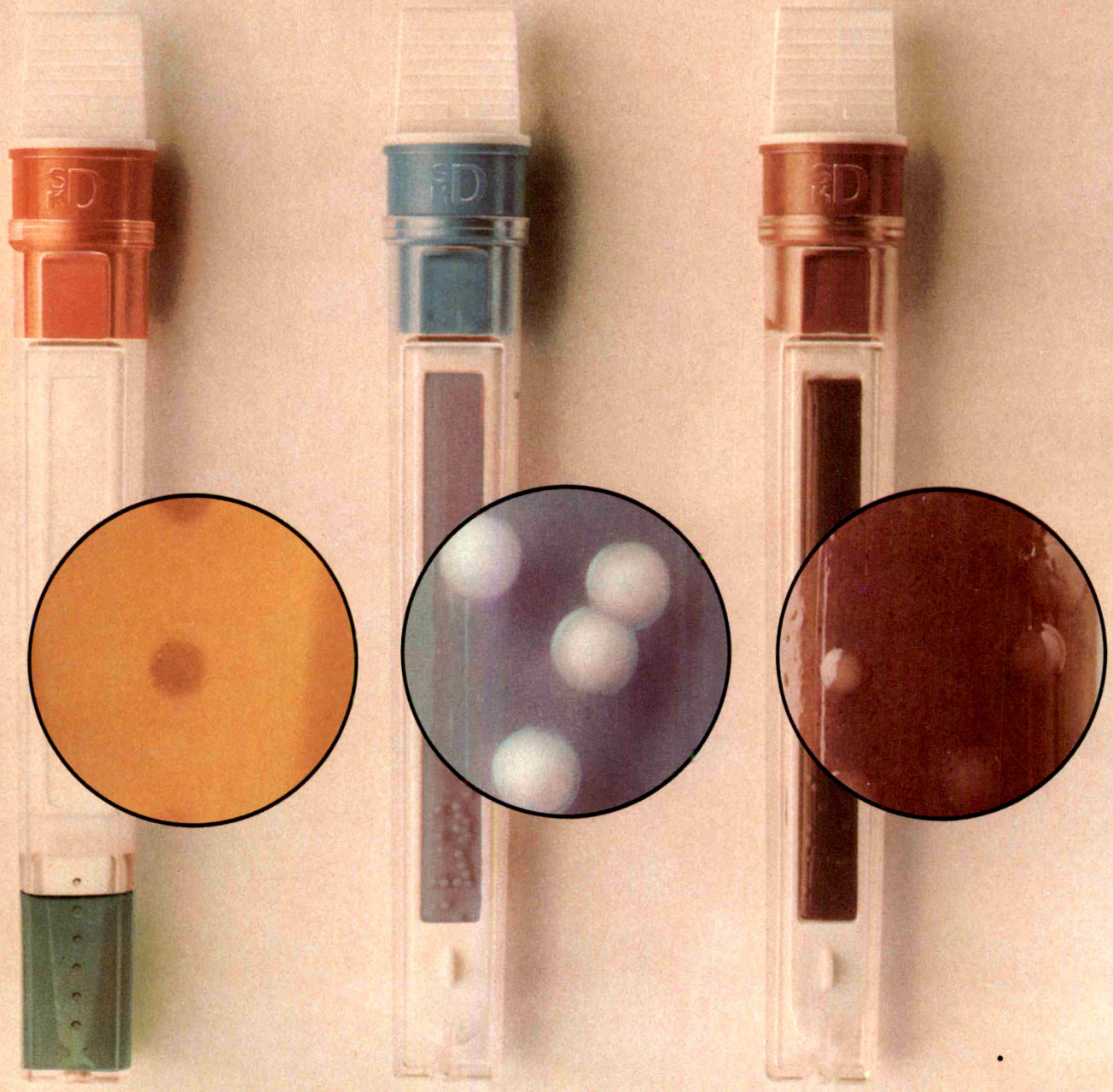
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A radioreceptor assay for human chorionic gonadotropin in normal and abnormal pregnancies: A clinical evaluation

ROBERT P. LORENZ, M.D.
BRUCE A. WORK, M.D.
K. M. J. MENON, PH.D.
Ann Arbor, Michigan

The human chorionic gonadotropin–radioreceptor assay (hCG-RRA) offers a rapid and accurate method of diagnosing early and abnormal pregnancies. Such a method is described along with clinical correlations in 139 assays done on 122 patients with amenorrhea, normal pregnancies, infertility, trophoblastic disease, ectopic pregnancies, and missed or incomplete abortions. The accuracy of the test is correlated with weeks of amenorrhea, weeks after ovulation, and clinical diagnoses. The overall accuracy of the assay was 95%. Those performed more than 28 days after the last menstrual period had an accuracy of 96.4%. There were no errors in the diagnosis of eight ectopic pregnancies among 33 suspected cases. Three patients are described who had serial changes from negative to positive early in pregnancy, providing data on precise timing of a positive result. Cases of missed abortion sometimes demonstrate a positive hCG-RRA after documented fetal loss. Recommendations for the most appropriate use of the hCG-RRA are presented based on the clinical experience at one referral center during the period January, 1977, to June, 1978.
(AM. J. OBSTET. GYNECOL. 134:471, 1979.)

THE INCREASED RELIABILITY of the human chorionic gonadotropin–radioreceptor assay (hCG-RRA) pregnancy test over the widely used urinary hemagglutination-inhibition tests has been previously documented.[1–3] Studies vary as to the assay technique employed, the resulting accuracy, and the clinical indications for the test. Based on laboratory data, Lee and Ryan[4] questioned the accuracy of the assay in very early pregnancy.

Landesman and Saxena[3] achieved good results using an assay technique which required repetition of a standard curve for hCG with each set of specimens. Fourteen serial hCG dilutions were used. Roy and associates[1] also had reliable results with an assay using a single reference serum of 100 mIU/ml hCG. An alternative method not requiring the routine use of such standard(s) is presented and evaluated.

From the Department of Obstetrics and Gynecology, University of Michigan.

Presented at the Forty-sixth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Kansas City, Missouri, October 13-15, 1978.

Reprint requests: Dr. Robert P. Lorenz, Department of Obstetrics and Gynecology, University of Michigan, Ann Arbor, Michigan 48109.

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The reported clinical accuracy of the hCG-RRA varies between 85% and 100%. The accuracy of our alternative assay is evaluated and compared to previous studies.

Suggested clinical indications cited in the literature include use with menstrual extraction, trophoblastic disease,[5] threatened abortion, infertility and ovulation induction, spontaneous abortion, ectopic pregnancy, and incomplete abortion.[1–3]

The following study is based on the clinical experience with the hCG-RRA used by the University of Michigan Gynecology-Endocrinology Laboratory from January, 1977, to June, 1978.

Material and methods

Partially purified plasma membranes were prepared from bovine corpus luteum by a method adapted from that reported by our laboratory.[6] A brief description follows: Approximately 20 gm of tissue was homogenized in 7 volumes of sucrose (0.25M) in a Dounce homogenizer. The homogenate was filtered through two layers of cheesecloth and the centrifuged at 400 g for 4 minutes. The supernatant was saved. The sediment was resuspended in 8 volumes of sucrose buffer,

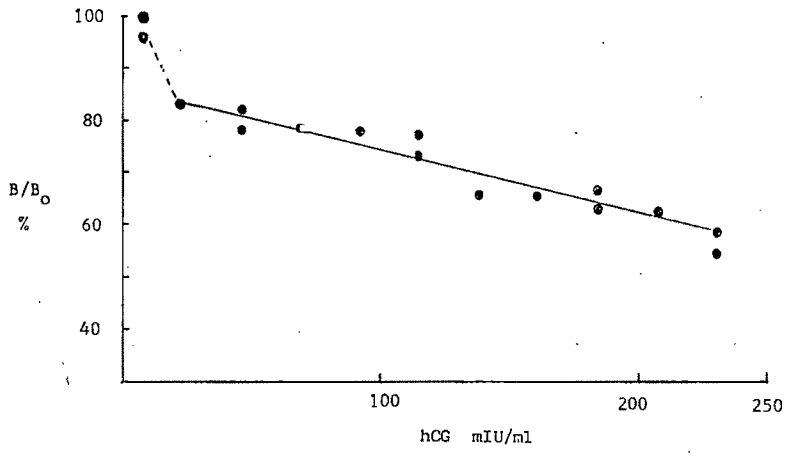


Fig. 1. Standard curve of hCG-RRA.

homogenized in a Dounce homogenizer, and centrifuged at 400 g for 4 minutes. The resultant supernatant was combined with the first supernatant and spun at 700 g for 10 minutes. The supernatant from the above was again centrifuged at 9,000 g for 15 minutes. The resulting sediment was homogenized in 50 ml of sucrose buffer. This fraction contained partially purified plasma membrane.

hCG (11,500 IU/mg) was iodinated by the procedure of Tsuruhara and associates.[7] The specific activity of the ^{125}I-hCG ranged from 40 to 60 cpm/pg.

The binding assay was performed by incubating 50,000 cpm of ^{125}I-hCG in 100 ml of buffer (10 mM Tris hydrochloride, pH 7.5, 1 mM calcium chloride, 0.1% bovine serum albumin) with 100 μl of the patient's serum sample and 40 μl of the membrane preparation. The volume of the incubation mixture was adjusted to 300 μl by the addition of the buffer. Incubation was performed at 37° C for 30 minutes and was terminated by the addition of 1 ml of buffer. The contents were then chilled in ice and centrifuged at 5,000 rpm for 20 minutes in a Sorval refrigerated centrifuge (4° C) using an SS34 rotor. The supernatant was then carefully decanted and the residue was counted in an automatic gamma counter. A control experiment was performed by incubating 100 μl of serum previously pooled from young, healthy women at midcycle. The pregnancy test was considered positive if the ratio of the radioactivity of the patient's serum to the control (B/B_0), expressed in percent, was less than 75%.

The sensitivity of the assay was redetermined at the end of the study period by a control experiment. Measured amounts of hCG (11,500 IU/mg) were added o normal male serum and then underwent the above assay. The results, B/B_0, are plotted against the concentration of hCG (milli-International Units per milliliter) in Fig. 1.

Clinical data were obtained from available medical records supplemented by patient interviews when necessary.

During the study period, January 1, 1977, to June 30, 1978, 503 patients underwent 535 hCG-RRA tests at the University of Michigan Medical Center Gynecology-Endocrinology Laboratory. Clinical data were available and analyzed for the study group of 122 patients undergoing 139 tests. The patient population was characterized by an average age of 27.5 years, average gravidity of 1.3, and average parity of 0.9. Thirty-nine percent of the patients were gravida 0, and 53% were para 0. The indications for the test according to the medical records (some patients had multiple diagnoses) were: rule out normal pregnancy, 61%; possible ectopic pregnancy, 30%; preoperative or preradiation, 7%; missed or threatened abortion, 5%; ovulation induction, 4%; and trophoblastic disease, 3%.

The following definitions were employed by Roy and associates[1] and will form the basis for a comparison with that study: (1) false negative rate: the percent of pregnant patients misclassified by the test; (2) false positive rate: the percent of patients not pregnant misclassified by the test; (3) clinical sensitivity: the percent of positive results when pregnant; (4) clinical specificity: the percent of negative results when not pregnant; (5) predictive value of a positive test: the percent of positive results that are true positive results; (6) predictive value of a negative test: the percent of negative results that are true negative results; (7) accuracy or efficiency: the percent of correct results both positive and negative of all tests performed.

Results

Clinical outcomes. As with most groups of patients undergoing pregnancy tests, the majority (58%) were not pregnant. Pregnancy continued beyond 20 weeks

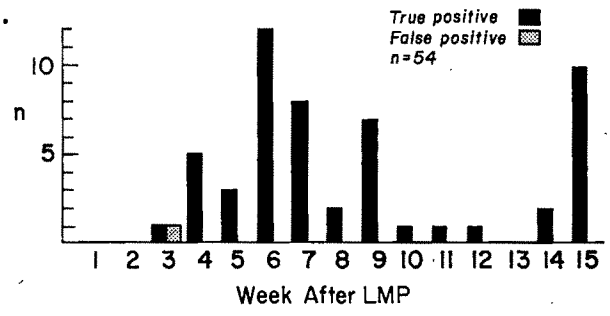


Fig. 2. HCG-RRA: Positive results versus menstrual age.

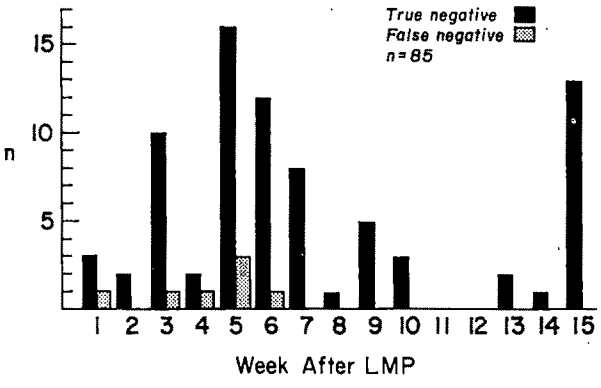


Fig. 3. HCG-RRA: Negative results versus menstrual age.

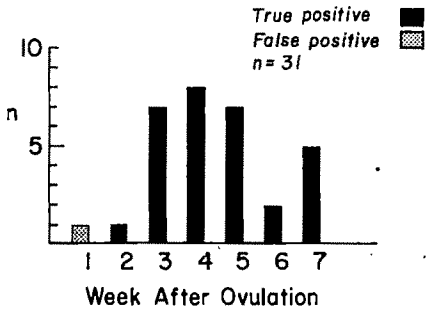


Fig. 4. HCG-RRA: Positive results versus ovulation date.

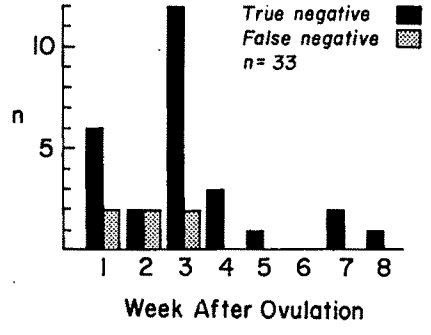


Fig. 5. HCG-RRA: Negative results versus ovulation date.

in 19%; spontaneous abortion occurred in 10%; elective abortion, in 7%; and 7% had verified ectopic pregnancies.

Accuracy. Because any pregnancy test depends on the stage of gestation, the patients were classified by menstrual history and, when available, history of date of presumed ovulation. The latter was determined by calculating the date 14 days prior to the expected menses in patients with very regular menses or by basal body temperature records when available.

Ninety-five percent of all hCG-RRAs done on the study group were accurate. Tests done after the twenty-eighth day following the last menstrual period, the usual time of the expected menses in most cases, were 96.4% accurate. During the third week after the last menstrual period, the accuracy was 85%—the commonly accepted accuracy of the standard urinary hemagglutination-inhibition pregnancy test at 6 weeks of amenorrhea. The accuracy of the hCG-RRA is shown according to menstrual and ovulatory history in Table I.

Patients with positive hCG-RRAs are classified by menstrual age in Fig. 2. Only one test was false positive, giving a false positive rate of 1.2%. This test occurred on menstrual day 15, possibly reflecting an unusually high midcycle luteinizing hormone (LH) peak which would confuse a receptor assay that reacts to elevation in either hCG or LH.

Patients with negative hCG-RRAs are classified by menstrual age in Fig. 3. Seven tests were false negative, resulting in an overall false negative rate of 11.7%. False negative results did not occur after 6 weeks of amenorrhea, the time when the standard urinary tests are just becoming reliable.

When those patients who gave a reliable history for the date of presumed ovulation were reclassified, the results were comparable. These results are shown in Figs. 4 and 5.

For the total study group, the sensitivity of the assay was 88%; the specificity was 99%; the predictive value of a positive test was 98%, and the predictive value of a negative test was 92%. The validity is assessed in Table II.

Ectopic pregnancies. Thirty-three patients underwent 36 tests for a diagnosis of possible ectopic pregnancy. There were no errors in this group: 23 were not pregnant, eight had clinically confirmed ectopic pregnancies, and two had intrauterine pregnancies documented at later elective abortion. Approximately 50% of this group had the study done within 28 days of the last menstrual period.

Early pregnancy. It is not unusual for the hCG-RRA to reflect accurately the presence of an early pregnancy before evidence appears on physical examination. This situation occurred in three cases in the study group, including one patient who underwent an ovarian cystectomy for a bleeding adenexa with a "normal-appearing" uterus at the time of laparotomy. A few

Table I. Accuracy of hCG-RRA

Day	Accuracy (%)	n
Menstrual history (days since last menstrual period):		
15-21	85	13
22-28	87.5	8
29	96.4	112
Ovulation history (days after ovulation):		
0-14	64	14
15-21	90	21
22	100	29

Table II. Validity of hCG-RRA (menstrual data)

	Days since last menstrual period			
	≤28	29-35	36-42	43≤
n	24	22	25	65
False negative rate (%)	33	50	8	0
False positive rate (%)	6	0	0	0
Sensitivity (%)	67	50	92	100
Specificity (%)	94	100	100	100
Predictive value (%):				
Positive	86	100	100	100
Negative	85	85	92	100

days later she passed pathologically confirmed gestational tissue.

Incomplete abortion. Minimal amounts of residual functioning trophoblastic tissue may be sufficient to maintain a positive hCG-RRA, even after viability of the pregnancy is lost. One patient presented with a clinical picture of complete abortion at 8 weeks of gestation and was managed conservatively with uterotonic drugs. She did well clinically and reported only minimal spotting for 4 days, during which time the hCG-RRA was positive on three determinations. On the fifth day she reported passing a small amount of tissue, and the hCG-RRA was negative on the following day.

Serial changes from negative to positive. It would be useful to know the exact timing of the conversion of the hCG-RRA from negative to positive during an early pregnancy. Three patients who were subsequently documented to be pregnant had closely spaced hCG-RRAs that converted from negative to positive. T. K. had a negative result on day 22 after presumed ovulation and positive results on days 23 and 30. D. A. had a negative result on day 14 after ovulation and positive results on days 16 and 21. L. H. had a negative result on postovulatory day 12, then a positive test on day 19.

Comment

The clinical specificity, the predictive values of positive and negative results, and the overall accuracy (efficiency) of this assay are comparable to the results of Roy and associates.[1] The false negative rate in early pregnancy, however, is higher. This could result from: (1) decreased sensitivity of this technique in early pregnancy or (2) more errors in reporting or recording the true last menstrual period. The former explanation is unlikely because the control experiment described documented the in vitro sensitivity.

In the cases of suspected ectopic pregnancy, the 100% accuracy of this study is an improvement over the false negative rate of 10% reported by Roy and associates.[1]

Any attempt to correlate the results of pregnancy tests done early in gestation with the stage of gestation is limited by the vagaries of menses, ovulation, and patient histories. For this reason data regarding date of presumed ovulation were studied as was menstrual history alone. The reliability of the test was approximately the same in both the ovulatory group and the menstrual group. If one accepts the ovulatory data, the conclusion might be that the test is somewhat less sensitive than the menstrual data indicate. However, the discrepancy may reflect only the increased difficulty in accurately determining the ovulation date.

Review of our clinical experience has led to some general guidelines for appropriate indications. All pregnancy tests suffer from a higher frequency of false negative than false positive results, so the two results should not be weighted equally. In any case no single laboratory test should be the basis for clinical management without appropriate consideration of the complete clinical picture. However, this study has reviewed numerous clinical situations where disregard for a positive hCG-RRA could be the basis for mismanagement. Early unruptured ectopic pregnancies, a corpus luteal cyst associated with an undiagnosed intrauterine pregnancy, and retained products of conception demonstrated positive hCG-RRAs. On the other hand, the sensitivity of the assay has prevented the use of this qualitative test to confirm the diagnosis of an inevitable abortion. The test has been positive after fetal death in our experience. The correct distinction between complete and incomplete abortion may be possible, but only if a few days have elapsed since the initial passage of tissue. In the management of trophoblastic disease, the hCG-RRA may be useful in initial diagnosis, but the qualitative assay for hCG-RRA often becomes negative while circulating hCG is still present as measured by the hCG β-subunit radioimmunoassay. Thus, in documented trophoblastic disease when speed is not critical, the more sensitive and no more costly hCG β-subunit assay is employed. We have noted an encouraging and marked increase in the use of the hCG-RRA by other medical services in our institution in patients scheduled for elective surgical, radiologic, or nuclear medicine procedures.

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Discussion

DR. FREDERICK K. CHAPLER, Iowa City, Iowa. Radioreceptor assays are based on displacement of labeled hormone from a receptor site by unlabeled hormone in the patient's serum or urine. It represents measurement of a biospecific hormone-receptor interaction and does not measure antigenic determinants on a hormone, as radioimmunoassay does. Consequently, it has great appeal to me because it measures an actual step in hormone action.

The authors have reported their experience with a qualitative radioreceptor assay for hCG. They described a new method, evaluated its accuracy, and gave some recommendations for its use. Their alternate assay method did not make use of routine standard preparations. Instead they used a sample of pooled LH peak serum as the control. This theoretically prevents false negative tests from arising due to an unexpected or midcycle LH surge (the radioreceptor assay does not distinguish between hCG and LH). The first question I have is concerned with the dose-response curve. The initial curve seemed displayed in an unorthodox fashion, but the revised curve looks more like a logit-log transformation. If this is so, it should be labeled as such. The method of determining a positive answer is a little confusing to me. Originally, the answer was based on a difference of 2,000 counts, between the control and unknown sample. This was changed to a percentage or ratio of B/B_0. Was this alteration due to a time-dependent loss of specific activity of the tracer or to some other problem concerning specific activity? Also why was an aliquot of the pooled LH peak serum not placed in each tube? What is the turnaround time, including counting time on the gamma counter? The literature usually states that this is under 2 hours and I would just like to know what the authors' time is.

The accuracy of this "yes/no" assay has been evaluated from several different and somewhat confusing aspects, but, in general, the authors' accuracy compares favorably with that reported in the literature. There is one point regarding the false negative analysis that needs clarification. It was stated that "when patients were classified on the basis of presumed ovulation the results were comparable." I am not sure to what they are comparable. The figure showing false negative values based on menstrual history indicated these to be seven of 85 while the figure of false negative values based on ovulation dating indicated six of 33. I think these can be compared, but they are quite different. Perhaps the purpose of that was just to show the vagaries of attempting to estimate a point in time based on a last menstrual period and/or a presumed ovulation.

The recommended indications for use of this assay seem appropriate, although some may doubt the clinical significance of being able to document the serial change of hCG from negative to positive. Perhaps this has value in treating patients with presumed luteal deficiency problems with progesterone suppositories. Since the assay is not quantitative, I agree that it has limited, if any, use in the management of trophoblastic disease or in threatened abortions. Much has been written concerning the radioreceptor assay's role in many abortions. Its high degree of accuracy on the first or second day of a missed menstrual period, as the author's have shown, should prevent most unnecessary procedures. Its use as a quick, sensitive, preoperative or preradiation pregnancy test will also be very valuable to the clinician. The radioreceptor assay for hCG seems very useful in the management of an unruptured tubal pregnancy and may well save some patients from laparoscopy and others from a laparotomy under emergency conditions. Certainly, this assay has to be compared with the beta-subunit hCG radioimmunoassay which is more sensitive but takes considerably longer, up to 48 to 72 hours. The radioreceptor assay's short turnaround time of 2 hours is a distinct advantage.

I would like to thank the authors for stimulating my interest in the radioreceptor assay, and I recommend the excellent review article by Saxena and Landesman[1] in the May 1, 1978, issue of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY. One final question to Dr. Lorenz: Have you had any experience with the commercially available hCG radioreceptor assay kit? Although its sensitivity limit seems to be a little high, I would appreciate any comments he might have concerning its use.

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DR. LORENZ (Closing). As Dr. Chapler has indicated, this laboratory technique for the hCG-RRA is a qualitative and more simple approach not requiring the usual hCG standards of previous studies.

Dr. Chapler's questions related to the original dose-

response curve and the determination of a positive result are based on a previous draft of this paper. Fig. 1 is a dose-response curve for the low concentrations of hCG found in early pregnancy. As the units and scale of the axes demonstrate, it is not a logit-log transformation. The abscissa represents the amount of hCG added to male serum in milli–International Units per milliliter. The ordinate is the ratio, expressed in percent, of the radioactivity of the standard serum, B_0. The curve demonstrates that a positive result, i.e., B/B_0 less than 75%, occurs in the range of 125 mIU of hCG/ml. This is the concentration of hCG that occurs in pregnancy at about the time of the missed menses. Expressing the results as B/B_0 does allow for time-dependent loss of specific activity of ^{125}I-hCG. Adding the pooled female sera to each assay would have transformed the result to $(B + B_0)/2B_0$ but would not have improved the reliability.

The comparison between the accuracy of the assay based on menstrual history to that based on ovulation data is valid when adjusted for the stage of gestation. By 6 weeks of amenorrhea 66 of 74 tests were correct, for an accuracy of 89%. Of the 46 tests done within 4 weeks after ovulation, 39 were correct, for an accuracy of 86%.

The serial changes from negative to positive results in three patients were offered not as an example of an indication for use of the hCG-RRA but as a demonstration of the timing of the earliest positive results in those cases.

We have not had an opportunity to compare our hCG-RRA with the commercially available method.

Information for authors

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Social problems of women patients in a private obstetrics and gynecology clinic

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Patients present or exhibit problems other than physical ones to their physicians and need access to some type of assistance for them. Over a 1 year period, women patients were referred to and seen by the medical social worker employed by a private obstetrics and gynecology clinic. Their social problems were studied by content analysis of patients' records, patients' social services cards, and monthly social services summaries. Results showed that 163 women exhibited 288 social problems consisting of three major types, financial, marital, and emotional. Various relationships were shown between the type of social problem and the primary reason the patient visited the clinic. It was also shown that if a patient has a financial problem, she is more likely to have a greater number of social problems than are other patients. (AM. J. OBSTET. GYNECOL. 134:477, 1979.)

WOMEN WHO WERE REFERRED over a 1 year period to a social worker employed by a private obstetrics and gynecology clinic were studied via content analysis in order to: (1) describe social problems that patients presented or exhibited, (2) explain how patients' ages and reasons for coming into the clinic were related to social problems, (3) determine whether or not financial problems are associated with social ones, (4) test the relationship between stress of illness, pregnancy, or infertility and social problems, (5) demonstrate that patients present more than physical problems to health care providers and (6) make it known that a social worker ought to be a part of the health care team.

This study deals with medical social work, a field where social work is practiced in a medical setting. Its primary responsibility is to help patients and their families deal with psychosocial needs which affect their abilities to adjust to illness or make optimum use of medical care.[1]

Medical social work deals with conditions that are disturbing to humans, including dependency, pain, mutilation, and death.[2]

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Methods

The data were obtained from each patient's social services card kept by the clinic social worker, from the patient's office record kept by the health care team, and from monthly summary sheets provided by the social worker. Information on the social services card was obtained both from personal interviews by the social worker and also from office records. The office record contained the patient's physical and personal history, laboratory reports, and notations made by the clinic staff after personal or telephone contact with the patient. (In this study the office record was used primarily to check reliability of the social services card.) The social worker's monthly summary sheets were a compilation of the frequency and types of social problems presented by the patients. (The original purpose of these sheets was to keep the physicians in contact with patients' psychosocial status; in this study the sheets were also used as reliability checks.)

The term "social problem" is used in this study to cover situations which caused discomfort or trouble to the patient. For instance, "divorce" is classified as a "social problem," although in actuality the situation of divorce may not be a problem to all subjects. Situations resulting in discomfort to some patients are also listed as "social problems," such as "infertility adaptation." In

Table I. Primary reason for patient visit to clinic at the time of referral to a social worker

Reason for visit	%*
1. Pregnancy-related	37
2. Surgery-related	21
3. Infertility-related	12
4. Other, including gynecologic complaints, routine examinations, emotional problems ("nerves"), suspicious Papanicolaou test, family problems, and sexual dysfunction	30
Total	100

*Number on which above percentages are based = 163.

Table II. Types of social problems of patients

Social problem	%*
Financial	32.5
Marital	19.6
Sexual dysfunction	14.7
Other	14.1
Family	13.5
Emotional	
General	12.3
Prenatal or postpartum	12.3
Presurgical or postsurgical	10.4
Unwanted pregnancy	10.4
Divorce or separation	7.4
Discharge planning	6.7
Adoption interview or information	6.7
Infertility adaptation, emotional	4.3
Grieving	3.7
"No show" with potential health danger	3.1
Absence of husband	2.5
Need for prenatal care	2.5

*Number on which above percentages are based = 162.

general, the term "social problem" is used here to delineate a problem other than a physical one presented by the patient or observed by a member of the professional health care team.

This sample consisted of 163 women who were referred to the social worker because they had a social problem. The number represents approximately 6.5% of the clinic patient population. The type of social problem was determined during the social work interview, involving the medical social worker (L. J. B.) and the patient.

Results

Two sets of results are discussed, including (1) descriptive, univariate analysis and (2) explanatory, bivariate analysis.

Single-variable descriptive results.

Age. Patients' ages ranged from 3 to 70 years, with a mean of 28 and a median of 26.

Medical staff person who referred patient to social worker. The modal referral source is Dr. A with 37% of the referrals, Dr. B refers 26% of the patients, and Dr. C, the newest physician, present only the second half of 1976, refers 6%; nurse-practitioners refer 10% of the patients; and the business office staff, 8%. The remaining 12% come from other sources, including office nurses, medical students, friends, or self-referral. The greatest percentage (69) of referrals thus come from the combined physician group.

Table III. Patients' ages by primary reason for visit in percentages*

Age (yr.)	*Primary reason for visit*			
	Infertility	*Pregnancy*	*Surgery*	*Other*
3-22	5	52	12	29
23-29	35	42	18	37
30-70	60	7	71	35
Total†	100	101	101	101
Numbers on which percentages are based	20	60	34	49

*$\chi^2 = 50.4$; $P < 0.0001$; $\lambda a = 0.19$.
†Totals do not equal 100 due to rounding.

Table IV. Percentage of patients with a financial problem by number of social problems.*

	No. of social problems		
	1	*2*	*3+*
Patients with financial problems	10	52	63
Numbers on which percentages are based	84	44	35

*$\chi^2 = 42.7$; $P < 0.0001$; $\lambda a = 0.19$.

Primary reason for visit to clinic at time of referral. The primary reasons for clinic visits are shown in Table I. The highest frequency of "other" occurs in 25 patients who came in with a gynecologic complaint. Ten came in for a routine examination, seven had an emotional or "nerves" problem, four did not visit the office after being informed of a "suspicious" Papanicolaou test, two had family problems, and one reported sexual dysfunction.

Types of social problems. A frequency distribution of the social problems presented by the patients is in Table II. It shows that the three most frequently occurring problems are financial problems, marital problems, and sexual dysfunction. "Other" and family problems follow closely in rank.

If all emotional or adaptation problems are combined into one category, then emotional problems become the largest category, representing 35% of the patients. Financial problems represent the second most frequent problem (33%). If marital and divorce or separation problems are combined, then this category rep-

Table V. Patients' social problems by primary reasons for visit in percentages

Social problem	*Primary reason for visit*				*Totals**	*Numbers on which percentages are based (of 163 patients)*	*Uncertainty coefficient (With social problem as dependent)*
	Infertility	*Pregnancy*	*Surgery*	*Other*			
Financial	2	59	19	21	101	53	0.10†
Marital	3	22	13	63	101	32	0.12†
Family	0	23	41	36	100	22	0.09‡
Divorce	0	67	33	0	100	12	0.16‡
Unwanted pregnancy	0	100	0	0	100	17	0.34†
Sexual dysfunction	8	8	17	67	100	24	0.14†
Emotional:							
General	5	0	0	95	100	20	0.39†
Pregnancy	0	100	0	0	100	20	0.37†
Surgery	6	0	94	0	100	17	0.49†
Infertility adaptation	100	0	0	0	100	7	0.55†
Grieving	0	67	33	0	100	6	0.13 (NS)
Discharge planning	9	36	36	18	99	11	0.02 (NS)
Adoption interview	100	0	0	0	100	11	0.65†
Absence of husband	0	50	0	50	100	4	0.08 (NS)
"No show" with health danger potential	0	40	0	60	100	5	0.10 (NS)
No prenatal care	0	100	0	0	100	4	0.22 (NS)
Miscellaneous social problems	0	61	17	22	100	23	0.08‡

*Totals do not sum to 100 due to rounding.
†P for χ^2 value <0.001.
‡P for χ^2 value <0.05.

Table VI. Most frequently presented social problems by primary reasons for visit in percentages.*

Social problem†	*Primary reason for visit*				*Total‡*	*Numbers on which percentages are based*
	Infertility	*Pregnancy*	*Surgery*	*Other*		
Marital, family, absent husband, and divorce	1	31	24	43	99	70
Financial	2	59	19	21	101	53
Emotional (combined)	14	31	25	30	100	64
Other (combined)	14	47	14	26	101	101

A total of 163 patients presented 288 social problems.
*$\chi^2 = 29.337$; $P < 0.001$; $\lambda a = 0.0037$.
†See Table V for original categories.
‡Percentages do not total 100 due to rounding.

resents the third most frequent type of social problem presented (27%).

Only one patient came in with sexual dysfunction as the primary (stated) reason for her visit to the clinic; however, in the interview by the social worker and/or physician, 24 patients reported sexual dysfunction. While only seven patients came into the clinic specifically because of "nerves," a total of 64 presented emotional problems.

Number of social problems per patient. The mean number of problems per patient is 1.76. Fifty-two percent of 163 patients have one social problem each; two problems are exhibited by 27%; and three problems by 16%; four problems are presented by 4%; and five problems by 1%.

Explanatory results. It is helpful to explain how some of the preceding items correlate.

Age by primary reason for visit to clinic. Table III shows that infertility patients are likely to be older; in the pregnancy-related group the opposite is the case. The surgery-related group appears to be older; the "other" group shows no relationship of age and reason for visit. The patients with pregnancy-related problems have the greatest frequency of being referred to a medical social worker at a young age and the oldest age referrals are in the surgery-related group.

Age by number of social problems. Using the Pearsonian r, age is shown to be weakly and inversely related to the number of social problems ($r = -0.15$, $P < 0.03$).

Financial problems by number of social problems. In Table IV it can be seen that association between financial problems and number of social problems exists. Those individuals who did not have a financial problem are more likely to have fewer than two social problems, while the individuals who had financial problems are more likely to have more than two social problems in

addition to their financial one. The data also show that while 14% of the entire sample has three or more social problems including a financial one, 8% of the 163 who do not have financial problems have three or more social problems.

Primary reason for office visit and number of social problems. There is no association between the primary reason for office visit and the number of social problems. However, if a patient comes to the clinic for infertility, the chances are greater that she has only one social problem (80% chance as compared to 43% in the pregnancy-related group, 53% in the surgery-related group, and 49% in the "other" group).

Primary reason for office visit and type of social problem. Table V shows that the infertility-related group ranks high in adoption interviews. The surgery-related group ranks high in family problems and surgery-related emotional problems. The "other" group ranks high in marital problems, sexual dysfunction, and general emotional problems, as well as in pregnancy-related cases with absence of husband. The pregnancy-related group holds the highest percentages in the problems of finance, divorce, miscellaneous, grief, prenatal or postpartum emotions, and "other reason for clinic visit" in absence of husband. Also the pregnancy group ranks high along with the surgery-related group in discharge-planning problems.

If four classifications denoting emotional problems from Table V are combined, and marital and divorce, financial, and other problems are grouped, another type of picture is seen (Table VI). Emotional problems appear to be evenly experienced by three of the four reasons for initial visit, with the exception of the infertility group. Financial problems are experienced the most frequently in the pregnancy-related group, which could also have been the main reason for referral to the social worker. Within the marital problems group, it is interesting to note that the "other" reason for clinic visit appears to be marital problems (which is more frequent than in the other groups). From Table V, sexual dysfunction also occurs more frequently in the "other" group.

Comment

A total of 163 female patients presented or exhibited to their physicians 288 social problems in 1 year. Since couples tend to seek help for their marital problems first from the clergy and second from their physicians,[3] there appears to be great value in making the services of a social worker available to help patients alleviate the distress and discomfort caused by social problems.

The "other" group of patients presented some interesting phenomena, such as high percentages of marital problems and sexual dysfunction in relation to other patients. Evaluating this group in terms of actual physical illness or the possibility of psychosomatic complaints by reviewing their clinic records a year later would show if significant physical pathology was ever found. The statistics presented by this group indicate that women do indeed go to their physicians for reasons other than physical complaints; they may in fact go to the physician with a variety of situational and emotional complaints as well. However, the patient appears not to come in with a complaint of a social problem but complains instead of a gynecologic problem. Perhaps she even chose a time of trouble to come in for her routine examination.

An association was also found between age and infertility-related reasons for visit and subsequent referral to the social worker. A possible explanation is that the infertility patient may be more worried and upset as she becomes older and still remains infertile. The infertility patient must have some wealth, as infertility tests and procedures can be quite expensive. The data did show that only 5% of the infertility group had financial problems.

In regard to the pregnancy-related group, it was found that as the patient became older, she was less likely to exhibit social problems. This might be explained that as a woman gets older, she may adapt to the stress of pregnancy and have less need for social services; also, the chances for pregnancy itself decrease as age goes over 30.

The surgery-related patients were older. This would be expected as the numbers of operations performed also increase with age, according to information from the physicians in the clinic. The "other" group appeared to show no association between age and the likelihood of social problems appearing although there was some peaking in the middle years.

We referred to a social readjustment rating scale and found that the problems of the women examined in this study were included in the top half (or highest ranking) of the stress scale.[4] High-stress events are pregnancy, personal injury or illness, sexual difficulties, change in financial status, divorce, marital separation, death of close family member, and change in health of a family member. No real statistical evidence was shown as to whether these life-event stresses cause or are possibly caused by stress. The patients who had social problems also had stresses. It was estimated that about 6.5% of the patient load of the clinic during 1976 experienced problems in relation to stress; stress may have caused social problems for some.

While only one patient came into the clinic for the primary reason of sexual dysfunction, a total of 24 ex-

hibited this problem. Perhaps individuals today still are reluctant to seek help for sexual problems.

A further study would measure and evaluate social services provided. A control group could be used to determine if social services do alleviate the problems of patients and, hence, the problems of illness.

We would like to thank the Boise (Idaho) Valley Obstetrics and Gynecology Clinic for their cooperation in providing subjects for this study.

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Discussion

DR. ROBERT M. KRETZSCHMAR, Iowa City, Iowa. It has been clearly demonstrated through this work that the social worker serves as a physician-extender in management of problems that significantly alter the health of the patient.

We have long recognized the presence of social workers in hospitals, particularly hospitals financed with state, county, or city support. This paper clearly describes how a social worker can function in the private health care arena in an outpatient situation.

I have reviewed the social service statistics for our Obstetrics Service during the year July 1, 1977, through June 30, 1978. During that period of time at the University Hospitals in Iowa City there were 3,083 deliveries. Single women made up 956 of this patient population. Forty percent of the deliveries were in teenage women. Of the total number of patients 675 had referrals to our Social Services Department. The majority of the referrals came from the patients or their families. Doctors accounted for only 75 of the referrals. Our Social Services Department, in reviewing charts, identified 494 additional patients who were in need of service and received service from our Social Services Department. This case finding was initiated by the social workers and done by reviewing in an ongoing fashion the patients' charts in our clinic and postpartum area. This indicates that roughly 40% of the services rendered by our Social Services Department was from cases not referred to the Social Services Department. I wonder if this same type of case finding could be employed in the private sector with the same type of results?

The total number of patients served on our Obstetrics Service was 38% of the total number of patients delivered. The types of problems encountered in the obstetric area were remarkably similar to those reported in this paper. The largest category was problems related to pregnancy of an unmarried woman, representing 693 cases, as a primary reason for Social Services contact. This was a secondary reason for service in 461 additional patients.

Problems in current functioning or relationships represented 110 primary reasons for Social Services contact and 398 secondary reasons for Social Services contact. Environmental stresses including financial need represented 162 primary reasons for Social Services contact and 126 secondary reasons for Social Services contact. Ambivalence or conflicts about parenting represented 30 primary reasons for Social Services contact and 71 secondary reasons for Social Services contact. There were additional problems that were managed by the Social Services unit with a total number of problems of primary and secondary categories totaling 2,705 problems.

Our social workers also reviewed charts for potential problems that fell into the same categories listed above but these problems were not managed by the Social Services Department. The total number was 1,477 potential problems. This indicates that we probably need more social work services in our Obstetrics Department. It also indicates that possibly in addition to those problems identified and treated by our social workers, there are a large number of problems which, through chart review, can be identified as potential problems, with potential patients in need of service. In the future could the authors try to review charts to identify social problems as reported in the record and thereby increase their effectiveness in the total comprehensive health care of the patients in their clinic?

DR. JAMES H. MAXWELL, Colorado Springs, Colorado. The authors have demonstrated the need for the services of social work expertise in dealing with the problems that appear in the clinical practice of obstetrics and gynecology. If anything, it is surprising to me that only 6.5% of their total clinic population had identifiable needs that resulted in referral to the social worker. One wonders if this low percentage would not increase as this particular team interacts with each team member and learns what role each fills. Adding further credence to this concept is the fact that financial problems (32%) and unwanted pregnancy (10.4%) are easily identifiable problems that are readily referred, whereas sexual dysfunction is apparently much more difficult to

detect and refer. (One patient was initially identified and referred, yet 24 patients eventually were identified as having sexual dysfunction upon referral and social worker interview.) What is true of sexual dysfunction is true of most of the other reasons for referral.

What the authors do not say in the paper is as important as what they do say, and what they do not say raises a multitude of questions in the mind of this reviewer.

There is no mention made of what criteria were used in establishing which clinic patients were referred to the social worker. One might suggest the use of a relatively simple inventory test such as that of Stewart at the University of Michigan.

The authors really do not establish the effectiveness of the social worker in the private context.

No mention is made of the model used by the social worker. Is the social worker more than a "unifier" for referrals? If so, what other function is served?

Also nothing is said of the goals of the social worker. Is initial evaluation, then referral, the only goal? I doubt it. Is correlation of services an additional function? No mention is made of the social worker's teaching function and counseling function and the dynamic interplay that exists between those two functions.

Finally, the authors do not discuss how long patients were seen by the social worker or how this therapy resulted.

As I said previously, "what the authors do not say in the paper is as important as what they do say." These "dark holes" in this paper (to borrow a term from astronomy) I am sure are proper subjects for future research and reporting. I, for one, eagerly look forward to seeing these "dark holes" filled in with light.

We are dealing, in our specialty, with women—many of whom are hurting, fearful, and troubled. Dostoevsky said, "Her's is a soul that has not yet found peace, and it must be treated gently because there may be a treasure in it."* The authors of this excellent paper have given us yet another tool with which to deal with the troubled soul we see daily in our clinics.

DR. JOHN COPPES, Albuquerque, New Mexico. Working with a Maternity and Infant Care Project, I am convinced of the need for a multidisciplinary team. Outcome statistics are often not good measurements of such efforts. Was there any study or anything shown in the pregnant women as to the improvement of prenatal care? Were there any more visits, and was the outcome of pregnancy changed in any way? In those pregnancies that were unwanted, was there any follow-up on child abuse or any problems of that nature in the unwanted child?

DR. LEE J. MONLEZUN, Lake Charles, Louisiana. I would like to share with the Association something that happened to me about 6 or 8 months ago. My brother is a psychiatric social worker, as well as a recent graduate of the Harvard School of Public Health; he returned to Louisiana to go into practice with me.

He entered my office, and he immediately began as a psychiatric social worker to see referred patients. He calls it a "psychosocial consultation." It is an ongoing consultation with my patients. Some 12 to 15 other obstetricians-gynecologists in town began to use him, and over the last 6 to 8 months he has acquired a tremendous practice.

I see patients at 6 month and 1 year intervals and have subsequently seen patients that I initially referred to him with much improved emotional and physical health.

It is like giving up a part of your practice, like stopping obstetrics and only practicing gynecology. A tremendous load has been taken off me. If one is looking for time off and for a person that can help, consider a psychiatric social worker.

DR. BROOKS RANNEY, Yankton, South Dakota. Since I practice in a region which is quite similar to that of the authors, it may be interesting to share with you a few general statistics concerning these problems which have been discussed.

First, most of our patients have real, physical problems which bring them to the obstetrician-gynecologist. Some may also have significant emotional problems. We do not have a social worker, but our obstetric-gynecologic "nurse-specialists," whom the patients may already know and trust, sometimes help us in the discovery and elucidation of these emotional problems. Most patients prefer that these be private, confidential discussions, only with their physicians.

Statistically, the problems we see fall into four major categories in the following order of frequencies:

1. Financial problems—severe debt caused by mismanagement or no management of the family budget, which results in severe family disharmony.
2. Alcoholism or drug abuse—primarily, in our area, alcoholism, usually by the spouse, but sometimes by the patient.
3. Sexual problems—various types of sexual incompatibilities between mates, or sexual infidelities, usually, but not always, committed by the man.
4. "Inconsiderateness" within the family—a lack of thoughtfulness concerning other members of the family which is often caused by a boorish, self-centered attitude by the husband, but sometimes is caused by a petulant, self-centered attitude by the wife.

These four categories of emotional problems are the ones most commonly seen in our region.

DR. GERALD B. HOLZMAN, East Lansing, Michigan. Several investigators in our area have demonstrated how cultural differences influence patient compliance.[1] Have the essayists in their analyses looked at the effect of cultural differences on the problems that they have enumerated?

*Dostoevsky, F.: The Brothers Karamazov, Part III, Book VII, p. 430.

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DR. ERNST R. FRIEDRICH, St. Louis, Missouri. What we are talking about is the realm of psychosomatic medicine. This is nothing new. When I was in medical school at the University of Heidelberg 25 years ago, we had a Chair of Psychosomatic Medicine. We have been trained (partially, at least) in psychosomatic medicine, but what we are all admitting now is that we do not train our medical students and our residents in this field. This is the reason why we are willing now to give up part—a very important part—of our practice to some paramedical personnel.

We are training more and more obstetricians and gynecologists, and some of us who are involved in their training are a little bit concerned whether we will have enough work for them in the years to come. Perhaps this is a field that we should get more involved in: Train our medical students and residents in psychosomatic medicine and do part of this important work ourselves rather than delegating it to others.

If other trained paramedical personnel are available, this is fine; they should be put to work. Maybe it is cheaper now, but we should also have in mind the long-term goals of our own specialty in the years to come.

DR. BARTON (Closing). I will attempt to answer several of the questions but will begin by saying that the last remark about our role in "psychosomatic care" and your training in this is a key issue. Many of us have not felt very comfortable in some of these things, either individually or in training. This is reflected in the attitudes of physicians in general, who express some skepticism about the value of paramedical personnel and specifically social workers in some of their roles in the health care team.

Dr. Kretzschmar had some very important statistics, from an institutionally related form of social work, particularly his methods of referral, physicians versus the surveillance system approach. Obviously, as was pointed out, only 6.5% of our total patient population were referred, and the majority were referred by physicians in private offices.

Others came from nurse-practitioners and office personnel. I am sure that if we had a surveillance system wherein charts were reviewed by the social worker more problems would be detected and, perhaps alleviated.

There would still be the question of physician acceptance of unsolicited review of charts as well as the question of financial reimbursement in offices that operate on a fee-for-service basis. We have found that some degree of explanation to the patient is necessary in our referral to a social worker as well as clarification and better communication with the social worker in resolution of the problems presented.

Statistics have been published dealing with what resources women consult for psychosocial problems and particularly marital problems. Members of the clergy are consulted first, physicians are second. Perhaps the definition of "physician" also would have to be considered.

Dr. Maxwell's question reflecting the 6.5% of our total population studied deals with the sensitivity of the physicians involved and their perceptions of problems of the patients; we all need to learn more about the sensitivity factor.

The things that we did not say certainly are important. Quantifying these data and making some effort to obtain more objective data in these fields are difficult. We are looking for suggestions as to how to do these effectively.

The perinatal team approach was commented upon, and it was questioned whether the prenatal care was improved and whether follow-up of unwanted children or unwanted pregnancy factors was done. In some instances referral to other community resources was utilized and in particular our maternal and infant care program supported by state and federal funds. Others were dealt with on an individual basis.

The discussion about the use of the psychiatric social worker reflects similar problems that can be approached in these workers' growing roles.

Dr. Ranney's comments about his ranking of the numbers of social problems as reflected in financial, alcohol and drugs, sexual, and family problems are also true in our cases. Alcohol and drugs per se might be objective factors underlying some of the emotional problems.

We did not deal with the compliance question and cultural differences, and again these would probably reflect our patient population versus that in other communities.

I think this study has served a specific purpose in attempting to quantify and assess the value of the social worker in a practice setting as well as to identify the frequency and the type of problem in that setting.

Once again, we are reminded of the fact that patients presenting physical complaints have a variety of underlying contributing factors of emotional and social adjustment. Personnel in a counseling capacity can serve as a valuable asset in dealing with some of these factors.

One-way maternal transport: An evolving concept

Inpatient services

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Transporting the high-risk pregnant woman to a tertiary center prior to labor or delivery, in an attempt to offer more intensive care to the patient and her infant, has gained increasing support from medical communities over the past few years. Because of this concept, tertiary centers need to be actively involved in the organization of these transport systems and to be certain that all members of the perinatal team at the referring as well as the receiving center are kept informed of events. This paper describes how Vanderbilt University Hospital initiated an active one-way maternal transport system and how that system is maintained and reviews the first 176 patients treated under that system. Establishing direct lines of communication between the practicing physician and the tertiary center and emphasizing continuing education at all levels seem to be important aspects in the development and maintenance of such a referral system. (AM. J. OBSTET. GYNECOL. 134:484, 1979.)

IN 1974, the Tennessee State Legislature passed a bill to allow the development of a plan that would implement a program for the diagnosis and treatment of certain life-threatening conditions present in the newborn infant and to establish a Newborn Advisory Committee. This legislation was the first step taken by the state to develop the regionalization of perinatal health care, a process defined as the organization of a region in which there are defined levels of perinatal care, consisting of at least one tertiary-level hospital whose primary concerns are education, communication, consultation, and transportation. This step was taken because Tennessee, when compared to the other states, ranked fourth from the bottom in infant mortality rate and because it had been demonstrated in other states that this process of regionalization could contribute to a lowering of the neonatal mortality rate. Arizona, by regionalizing neonatal intensive care units, reduced its infant mortality rate from forty-third to eleventh in this country during the five years from 1967 to 1972.[1] The Tennessee Newborn Advisory Committee established newborn care guidelines and did much in other areas to attempt to reduce neonatal deaths. The neonatal mortality rate in this state dropped from 16.2/1,000 in 1970, to 11.6/1,000 in 1976.[2] In the same period the infant mortality rate fell from 21.3/1,000 to 16.1/1,000, equal to the national rate in 1976.[2] Through further legislation in 1977, this committee was expanded to encompass obstetric concerns and is now known as the Perinatal Advisory Committee. Although somewhat delayed in becoming actively involved in the regionalization process, the state's Obstetrical Society recently came out in favor of regionalizing perinatal health care.

While the pediatricians had a great deal of experience in setting up the various aspects of regionalization, there was no clear mechanism to guide the obstetric side. In 1975, therefore, a 2 year grant was given to Vanderbilt University Hospital to design and implement a plan to effect obstetric regionalization in middle Tennessee, a 37 county area with a population of 1,270,000 and approximately 22,000 deliveries per year. From the beginning it was clear that one of the methods for lowering the neonatal mortality rate was the establishment of a two-way newborn transport system. Nevertheless, after a review of the data from the neonates transported to Vanderbilt, it seemed that many of those brought by the transport van could have been more safely transported in utero had there been a mechanism by which the mother could be easily re-

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ferred to the tertiary center prior to delivery. Therefore, while a great deal of emphasis was placed on establishing numerous nursing and physician continuing education programs on modern obstetric subjects, and while certain consultative services such as the establishment of a Xerox Telecopier Network[3] were made available to hospitals and physicans in the area, this report will discuss those plans which led to an active one-way maternal transport system in middle Tennessee and how that system was implemented and will present a summary of the maternal transport patients admitted to Vanderbilt from July 1, 1976, to July 1, 1977.

The plan

The fault of many programs originating from tertiary centers seemed to be poor communication between the institutions involved. Physicians in small community hospitals often expressed concern that members of the tertiary center's "ivory tower" could not understand their needs or situations and, consequently, would not willingly respond in a positive fashion to various programs proposed by the tertiary center. Therefore, it seemed imperative to visit each hospital in middle Tennessee offering obstetric care so as to identify specific needs and problems in the area and to open lines of communication. Accordingly, funds were obtained through the Regional Medical Project to hire a highly specialized obstetric nurse to visit the 46 hospitals in middle Tennessee that give obstetric care. After arranging the initial visit by telephone or letter the nurse went to each hospital to survey the obstetric facility, to gather as much information as possible, and to schedule an all-day meeting at a later date with the hospital administrator, the director of nursing, the head nurse of obstetrics, as many of the local physicians practicing obstetrics as possible, herself, and the senior author (F. H. B.). Such an arrangement allowed the reviewers to be better informed concerning the various local medical and political situations prior to discussing with these physicians the regionalization concept.

At these second meetings, regionalization of perinatal health care was explained and copies of the document entitled "Towards Improving the Outcome of Pregnancy,"[4] prepared by The American College of Obstetricians and Gynecologists, The American Medical Association, The American Academy of Pediatricians, and The Academy of Family Physicians, were given to each person attending the meeting. The physicians were told that if they had any obstetric problems on which they wanted consultation, they could call 24 hours a day and speak to a full-time faculty member. This point was important since it seemed that private physicians felt more comfortable consulting with (or possibly transferring patients to) another private physician. This system would help circumvent problems that arise when a referring physician speaks to medical personnel with perhaps less training than he or she has or with whom the physician is unacquainted and may not, in fact, trust. Physicians were told that Vanderbilt Hospital would not turn away any obstetric emergency and that every attempt would be made to keep patient expenses down. Furthermore, emphasis was placed on our desire to give rapid, detailed follow-up information to the referring physician and institution since many physicians felt the lack of follow-up was a major deficiency in tertiary center care. The task then facing the tertiary center was to be certain that when consultation occurred it would comply with the verbal commitments made at these visits.

High priority had been given at each visit to continuing education for nurses and physicians in the area. A position, therefore, was created for a second highly trained and specialized registered nurse who could effect and coordinate the consultative and educational commitments of regionalization. Such an individual was important not only for the educational aspects of a regionalization project but also to help implement a continuing liaison between the various hospitals and physicians and the tertiary center. In particular, two outstanding concepts of this job were: (1) outlying hospital visits and (2) in-hospital (tertiary center) duties. Outlying hospital visits included educational programs for nurses in which such subjects as fetal monitoring, high-risk obstetrics, and other related topics were openly discussed. Physicians at the potential Level I and Level II sites were occasionally visited to review problems, to give follow-up information for previous consultations or referrals, to give out information about services available at the tertiary center, and to communicate to the physicians that the tertiary center continued to be actively interested in events in their areas. Hospital personnel were also given follow-up information on patients they had transferred to the tertiary center. Finally, public relations in the local area was an important part of this job inasmuch as local consumer needs could best be met by active communication between the tertiary center and the area served.

In-hospital or tertiary center responsibilities revolved around three important aspects. The first of these was to coordinate the transfer of patients from Level I or Level II hospitals to the tertiary center, assuring that this transfer was without significant technical problems and helping members of the patient's family make the emotional transition from local hospi-

Table I. Location of referrals

	No.
Referring cities	42
In-patient referrals:	176
For delivery	169
For other reasons	7

A total of 35 cities sent one to five patients; four cities sent six to 10 patients; two cities sent 11 to 15 patients; one "city" sent 46 patients (military base).

Table II. Indications for referral*

Indication	*No.*
Premature labor	58
Premature rupture of membranes	32
Hypertension of pregnancy	25
Rh disease	16
Twins	11
No facilities for delivery or cesarean section	9
Chronic hypertension	8
Third-trimester bleeding	8
Compound or breech presentation	7
Diabetes mellitus	6
Abruptio placentae	8
Amnionitis	4
Postpartum hemorrhage	3
Polyhydramnios	3
Intrauterine growth retardation	2
Postdates	2
Insufficient cervix	2
Possible genital herpes	2
Fetal anomalies	2
Placenta previa	1
Eclampsia	1
Ruptured uterus	1
Maternal hepatitis	1
Failure to progress in labor	1
Fetal arrhythmia	1
Molar pregnancy	1

*Some patients had more than one indication for referral. Total babies delivered: 180. Total live births: 163.

tal care to medical center care. These tertiary level duties also involved a series of mechanisms such as helping the patients be admitted to the hospital, following up all tests that were done, and, finally, seeing the patient each day to provide a sense of continuity of care. Second, the nurse-coordinator kept records on all in-patient consultations and communicated by phone with the referring physicians at each stage of the patient's progress. A final letter after delivery was written to the physicians giving details of the patient's course. Third, this coordinator gathered educational material to be distributed to the nurses and physicians delivering obstetric care in middle Tennessee to keep them abreast of the newer techniques and advances in obstetrics. At the present time there are two such regionalization nurses performing the duties outlined above, with one being responsible for in-house tertiary center duties and the other handling the outlying hospital educational visits. Certain overlapping in all these responsibilities obviously exists.

Results and comment

Beginning July 1, 1976, formal records were kept on all patients transported to Vanderbilt Hospital for intrapartum or postpartum care. From July 1, 1976, to July 1, 1977, a total of 176 patients, from 42 cities, were transported to Vanderbilt University Hospital for problems arising in the intrapartum and postpartum periods (Table I). Prior to this time approximately one to two patients were transferred to Vanderbilt Hospital each month. These patients came by car, ambulance, or helicopter from various sites throughout Tennessee and the southwestern section of Kentucky. Ten patients were sent from regions in Tennessee other than the middle perinatal region, 58 were from southwestern Kentucky, and the remaining 108 patients were sent from the middle Tennessee area in which Vanderbilt serves as the tertiary level hospital.

As can be seen in Table I the military base in our area transported the largest number of high-risk pregnant women with 26% of the total number of patients referred. This is not surprising since, for many years, military medicine throughout this country has triaged patients to tertiary centers even before regionalization or maternal transport concepts were widely discussed and developed. As the benefits of this type of program become known, more acceptance by nonmilitary medical personnel will occur and the number of civilian transports will continue to increase.

After reviewing the patient's problem with the referring physician by phone, the patient and her family were sent directly to the Fetal Intensive Care Unit, bypassing the more inconvenient emergency room admission route. The nurse regionalization coordinator met each family as soon after arrival as possible to assist them in becoming settled in their new environment. Work-up was done by the house officer on duty, and the senior author (F. H. B.) or his associate reviewed each case after admission, discussing the problem at length with the patient and her family not only to impart information but also to help reduce anxiety levels. After delivery, the referring physician was notified by phone by either the senior author or the nurse-coordinator, with emphasis being made on sharing educational information. This phone call is extremely important as it keeps the referring physician involved in the team effort as well as allows him to be fully informed if the patient's family calls him for further information.

Table III. Tests performed (maternal)

Test	*No.*
Fetal monitoring	169
Amniocentesis	52
Ultrasound	51
Culture and sensitivity:	40
Cervix	23
Amniotic fluid	11
Placenta	5
Blood	1
Lecithin/sphingomyelin ratio	37
Kidney–urinary tract–bladder roentgenography	12
Oxytocin challenge test	10
Estriol level	4
Electrocardiogram	4
Amniotic fluid creatinine	4
Delta optical density	3
Amniogram	2
Intravenous pyelography	1
Echocardiography	1
Maternal chromosome evaluation	1
Real-time ultrasonography	1
Amnioscopy	1

Table IV. Type of delivery

Delivery	*No.*
Vaginal	113
Cesarean section	56
Total	169

Of the listed indications for referral (Table II), 90 were for premature labor or premature rupture of membranes. As referring physicians became acquainted with newer techniques in treating such disorders, such as the use of beta-mimetic drugs to stop contractions[5] and the use of steroids to accelerate lung maturity,[6] it was hoped that the philosophy of the referrals would change. Patients are also referred to the Level III center for tests and techniques that are not available in the smaller community hospital (Table III). As fetal monitoring gains more acceptance and becomes more readily available in Level I hospitals, the high-risk patients referred merely for this technique, either prior to or during labor, will decrease.

Table IV reveals that of the 169 patients transported for delivery, 56 (33%) underwent cesarean section. This percentage is not unexpected in such a high-risk population and compares to an overall 12% cesarean section rate in the hospital. Five-minute Apgar scores reveal that the majority of neonates are delivered in good condition with 139 (77%) having scores in the 7 to 10 range (Table V). Thirteen neonatal deaths occurred in this high-risk group (Table VI), for a neonatal mortality rate of 79.3/1,000 compared to an overall

Table V. Five-minute Apgar scores

Classification	*No.*
Normal (Apgar score 7-10)	139
Moderately depressed (Apgar score 4-6)	13
Severely depressed (Apgar score 1-3)	7
Stillborn (Apgar score 0)	17
Apgar score not available	4

Table VI. Neonatal deaths

Case No.	*Weight (grams)*	*Maternal/neonatal diagnosis*
1	397	Polyhydramnios/prematurity
2	595	Polyhydramnios/prematurity
3	652	Prematurity (respiratory distress syndrome)
4	709	Hyaline membrane disease
5	794	Prematurity (respiratory distress syndrome)
6	800	Hyaline membrane disease
7	1,417	Hyaline membrane disease
8	1,503	Hyaline membrane disease
9	1,871	Multiple congenital anomalies
10	2,268	Group B β-hemolytic streptococcus
11	2,495	Hyaline membrane disease and group B β-hemolytic streptococcus
12	Weight not available	Rh disease
13	Weight not available	Eclampsia/asphyxia

Summary: <1,000 grams, six deaths; 1,000 to 1,500 grams, one death; 1,501 to 2,000 grams, two deaths; 2,001 to 2,500 grams, two deaths; >2,500 grams, no deaths; weight not available, two deaths.

neonatal mortality rate of 11.6/1,000 in Tennessee in 1976.[2] Listed also are a wide range of neonatal complications, confirming that these high-risk neonates often require intensive care at a high-level facility (Table VII). A diagnosis of prematurity was made in 90 of the 163 live-born babies (55%).

As can be seen in Table VIII the average weight of the babies was 2,293 grams or 5 pounds, with 12 neonates weighing less than 1,000 grams and 64 weighing more than 2,500 grams. The majority of the neonates, therefore, ranged in weight from 1,000 to 2,500 grams (56%). Six weights were unavailable. Recent reports[7] indicate a 30% to 60% survival rate in the 600 to 1,000 gram range. Six of the twelve neonates in this series weighing less than 1,000 grams died, for a survival rate of 50% (Table VI), representing a signficant advance in neonatal survival in this weight category over the past ten years, and indicating a need for a change in attitude toward the premature fetus. Currently, we are treating

Table VII. Neonatal complications

Complication	*No.*
Prematurity	90
Hyperbilirubinemia	36
Respiratory distress, type II	24
Dysmaturity	15
Hyaline membrane disease	14
Neonatal death	13
Erythroblastosis	11
Sepsis	6
Pulmonary edema	6
Anomalies	6
Hypoglycemia	6
Infant of diabetic mother	5
Patent ductus arteriosus	5
Necrotizing enterocolitis	4
Asphyxia	4
Anemia	4
Meningitis	4
Intracranial hemorrhage	3
Pneumonia	3
Acidosis	2
Hypocalcemia	2
Hepatic laceration	1
Pneumothorax	1
Cardiopulmonary arrest	1
Rash	1
Persistent fetal circulation	1
Hemophilus influenzae	1
Cephalohematoma	1
Primary apnea	1
Oral monilia	1
Congenital torticollis	1
Scalp abscess	1
Polycythemia	1
Brachial plexus injury	1
Congenital hip dislocation	1

Table VIII. Birth weights

Range (grams)	397-4,536
Average weight (grams)	2,293
Weights unavailable	6
<1,000 grams	12
1,000-1,500 grams	20
1,501-2,000 grams	35
2,001-2,500 grams	43
>2,500 grams	64

Table IX. Stillbirths

Case No.	*Weight (grams)*	*Associated factor*
1	500	Premature rupture of membranes (27 hr) and abruptio placentae
2	680	Multiple congenital anomalies
3	822	Pregnancy-induced hypertension and undiagnosed Rh disease
4	970	Abruptio placentae
5	1,389	Pregnancy-induced hypertension, positive oxytocin challenge test, chronic abruptio placentae
6	1,474	Multiple congenital anomalies
7	1,559	Second twin with prolapsed cord
8	1,588	Fetal death 4 wk. previously, unknown etiology
9	1,644	Pregnancy-induced hypertension
10	1,729	Abruptio placentae
11	2,381	Premature rupture of membranes × 3 days with septicemia
12	2,410	Premature rupture of membranes (loss of fetal heart tones in labor—true knot in cord)
13	2,778	Pregnancy-induced hypertension
14	3,240	Multiple congenital anomalies
15	3,515	Automobile accident—abruptio placentae
16	3,799	Rh disease
17	Weight not available	Fetal death 37 days previously, unknown etiology

Summary: <1,000 grams, four deaths; 1 000-1,500 grams, two deaths; 1,501-2,000 grams, four deaths; 2,001-2,500 grams, two deaths; >2,500 grams, four deaths; weight not available, one death.

a 28 week gestation as aggressively as a term gestation.

Table IX reviews the 17 stillbirths. Fifteen of this number were dead upon arrival at our institution and represent a group of patients where delay in transport or consultation may have played an important role in the overall outcome. Multiple congenital anomalies occurred in three of the total group (17.6%), while five cases (29%) were associated with abruptio placentae. Therefore, approximately 47% of the stillbirths can be listed as nonpreventable; however, the majority (greater than 50%) may have been prevented if consultation and/or maternal transport had been undertaken prior to the fetal death. Educational aspects of regionalization continue, therefore, to represent a major aspect of our overall middle Tennessee program.

Because of the rising medical costs there is a continuous awareness of the economic burden placed on the patients who are transported from the surrounding communities. Consequently, it was reassuring to note that the average hospital stay of the patients delivered vaginally was only 4 days and that of those undergoing cesarean section was only 8 days (Table X). Every attempt was made to send the patient home early or back to the referring hospital for recovery in an attempt to hold down these costs. The average neonatal stay was 8 days (Table XI), with only 14 neonates requiring a

Table X. Duration of maternal hospitalization

Total patients (No.)	169
Total stay in hospital (days)	976
Range of stay in hospital (days)	1-24
Cesarean section:	
Total (No.)	56
Average stay (days)	8
1-5 Hospital days (No.)	7
6-10 Hospital days (No.)	38
<10 Hospital days (No.)	11
Vaginal delivery:	
Total (No.)	113
Average hospital stay (days)	4
1-5 Hospital days (No.)	92
6-10 Hospital days (No.)	19
>10 Hospital days (No.)	2
Hospitalized for other reason:	
Total (No.)	7
Average hospital stay (days)	4
1-5 Hospital days (No.)	6
>10 Hospital days (No.)	1

Table XI. Duration of neonatal hospitalization

Total babies (No.)	160
Total stay in hospital (days)	1,305
Range of stay in hospital (days)	1-68
Average stay in hospital (days)	8
Died in delivery room (No.)	3
1-5 Hospital days (No.)	84
6-10 Hospital days (No.)	45
11-20 Hospital days (No.)	14
>20 Hospital days (No.)	14

hospitalization of longer than 20 days. Many of the neonates were also referred back to their home hospitals for growth after the initial stabilization period was past. Follow-up on the hospitalization required at the referring institution is unavailable.

A formal letter outlining the care given (Tables III and IV) and the results (Tables V, VI, and VII) was sent the day following discharge. Patients were instructed to return to their own physicians for postpartum care unless specific reasons such as related specialty consultations or follow-up testing necessitated further visits to the tertiary center. Whenever possible, the majority of antepartum care was given at the referring site and the patient was transported to the tertiary center for delivery only.

Currently the Vanderbilt Fetal Intensive Care Unit is receiving approximately one in-patient referral per day from middle Tennessee and surrounding areas. An update of our data indicates that while only 176 maternal transports occurred in 1976, 253 patients were transported in 1977, and in the first quarter of 1978, 108 patients have been sent to the tertiary center for delivery. It has been obvious that as lines of communication have opened, physicians have responded positively and are consulting frequently on complicated obstetric cases. That such a maternal transport system can work was noted by Harris and associates[8] in Arizona who reported that the neonatal mortality rate was lower for the maternal-fetal transports than for newborn transports in comparable groups of mortality risk.

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Discussion

DR. JOHN B. NETTLES, Tulsa, Oklahoma. In the development of regional systems for the improvement of health care the pediatricians are farther along than are the obstetricians. The authors have presented quite clearly a concept that will help most of us who are trying to develop a regional system of obstetric care. I emphasize "regional system" rather than "regional center," for what is needed is not merely a transfer of patients with complications to a sophisticated center, but rather a system that involves everyone concerned, with each person and each facility doing what it can best do. Although the Vanderbilt University Hospital makes a major contribution to the reduction of morbidity and mortality rates through their sophisticated personnel facilities, I suspect that an even greater contribution to their program, and to us, is in their humanistic approach and their efforts to improve

communication. Dr. W. P. Gideon, a member of our faculty, observed that this paper might be entitled "Toward an improved outcome of communication."

It is gratifying to see the key role the nurse has in the program in such critical areas as establishing rapport with the hospitals in the area, giving emotional support to the patients and their families, learning about and correcting problems throughout the area, developing appropriate continuing education programs, bridging the "town/gown" gap, assuring a continuum of care, and keeping the referring physician up to date on developments. I understand that Ms. Haire is accepted by the referring physician as well as is Dr. Boehm and probably much better than a member of the house staff who happens to be on duty at the time. This program is a fine example of the collegial relationship between our disciplines that is fostered by such groups as the Nurses Association of the American College of Obstetricians and Gynecologists.

In the Tulsa area we have increased our use of maternal transport and while at present our experience cannot be easily evaluated from the statistical standpoint certain facts are obvious. Perhaps the most noticeable changes are in the profile of the obstetric services in the referring hospitals and the economic impact. For instance, one major hospital in our referral area had several case presentations for each monthly perinatal morbidity and mortality conference prior to our increased use of maternal transport. Now the hospital has such conferences quarterly or less frequently because of the tremendous decrease in neonates with complications. Another shift has been in the number of days of high-cost, long-stay neonates. This would not be of as much importance if these costs were paid for by third parties, but when the proportion of inability to pay is unusually high in those patients transferred the tertiary hospital must find some way to recoup the added costs. We too have used maternal transfer in both directions, for example, one of the Indian Health Service hospitals may refer a patient to Saint Francis Hospital which houses the Eastern Oklahoma Perinatal Center for delivery. The patient and perhaps her infant may be returned to the Indian hospital as soon as practical, thus making a lesser dent in contract health funds and enabling the Indian Health Service to offer more services to other patients.

In summary, it is refreshing to see a joint paper by a physician and a nurse before this association and their teamwork in developing a program that should help all of us who are following in their footsteps. I would like to ask three questions: (1) What is the secret for obtaining legislature support? (2) How cost effective is the Xerox Telecopier Network? (3) What problems, if any, have occurred with the shifting of costs of those unable to pay—primarily to the tertiary hospital?

DR. LEE B. STEVENSON, Farmington Hills, Michigan. I have deliberately avoided bringing the Michigan experience into this discussion as well as neglected the Michigan adaptation of "Towards Improving the Outcome of Pregnancy."

The wooing and winning of physicians' patients in central Tennessee by the Vanderbilt system is mindful of a quote from "Anna and the King of Siam": "Et cetera, et cetera, et cetera" or education, transportation, communication; education, transportation, consultation; education, transportation, communication. Repetition of each of these is vital to the success of such a lifesaving venture.

Their plan and results are adequately described. The military's use of the program makes one wonder how many of the consultations or transports were on a Friday afternoon or prior to a holiday. This "dumping" has been a problem in other communities as a convenience for the too-busy practitioner.

Another question raised by the presentation is whether the primary physician has privileges at the tertiary center for any or all of the components of his patient's care. The text is hazy on this aspect but leads me to believe that no such provision exists.

Education seems to be the second key to reducing the number of referrals without adversely affecting the perinatal mortality and morbidity rates. Results of some studies show that the outcome for the referred parturient and her infant are often not as bad as anticipated.[1] In the Goodlin[1] study in California, only 18 of 200 transferred cases required neonatal intensive care facilities.

Two areas of concern were not specifically addressed: One is the product and the second is the cost. What is the quality of the infant in childhood and adolescence and as an adult? We are constantly harangued from all sides about the perinatal mortality rate, the problems of prolonged institutional care, and the cost of this care. But what is the end product, or "the bottom line," of our extra efforts in this perinatal jungle?

Is the expense justified? Is the concept truly cost effective? Costs at Level I or Level II community hospitals cannot be compared to the excessively high and often inadequately reimbursed expenses at a Level III center. Third-party payment programs require cost accounting and no satisfactory method recognizes program advantages of comprehensive perinatal care for mother and infant, even when the perinatal period is essentially uncomplicated. As Dr. Hermann Ziel has pointed out in some of his talks on regionalization in Michigan, "Third party payment programs have failed to recognize the cost of many important program elements in their reimbursement methodology." The problem is particularly acute in regional centers which serve as the focal point for planning, implementing, and evaluating comprehensive perinatal care. Unfortunately, there is little hope that regionalized perinatal care can be financially feasible for either the physician or hospital until this situation is corrected. Both the Vanderbilt program and the Arizona program had

special financial arrangements which allowed feasibility.

In the booklet "Towards Improving the Outcome of Pregnancy," financing of regionalization is addressed and the generation of new costs by improved care and technology is recognized. Costs will be increased by education and training of personnel. The providers of services, "both individual and institutional, must increase their effort and proficiency in identifying actual costs and in relating these to the benefits in terms of morbidity and mortality."[2]

Do the authors have any comments on the financing of perinatal care—which includes maternal and neonatal care? Are late follow-up studies on the "product" a part of the Vanderbilt study?

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2. The National Foundation/March of Dimes: Towards Improving the Outcome of Pregnancy, Recommendations for the regional development of Maternal and Perinatal Health Services, New York, 1976, Committee on Perinatal Health.

DR. I. RAY KING, Knoxville, Tennessee. As of September 1, 1977, I assumed the directorship of the East Tennessee Regional Obstetrical Program. I went through the literature trying to find how to implement a regional obstetrical program and there were very few articles describing such a program. One of the first ventures was to go with my regional obstetrical nurse to Vanderbilt and spend a day with Miss Haire and Dr. Boehm. This has been very rewarding and I would like to relate a few things that have happened.

In the eastern Tennessee region we have some 16,000 deliveries. In the first 9 months of our consultation and referral service, we have had 59 maternal transports to the University Hospital in Knoxville and 53 outpatient consultations. I do not have figures on how many were referred prior to this time, but there were no more than one or two maternal transports per month.

I would like to emphasize a few things. The personal relationship that Dr. Boehm has described is of ultimate importance. We now know most of the people in East Tennessee who deliver obstetric care on a first-name basis. We have done this in 1 year's time and this is the keystone of our acceptance.

Also we at the tertiary center have to accept that we are going to have many uninteresting, even though challenging, problems, such as premature rupture of the membranes and premature labor. We have a few "interesting" patients but most deliveries are routine. Those of you who may enter into a regionalization project at the tertiary level will have to accept some humility, realizing that many of the patients referred are not referred because our delivery method is better than others but because of the neonatal center.

There are two problems I would like to address. One has to do with providing enough staff to accept the consultations and referrals. We did not have on our full-time staff an adequate number of obstetricians. We solved this problem by persuading eight physicians in our city to accept this responsibility and through our grant they are paid 50 dollars per day. This may seem like a large payment, but when a patient is referred, she is charged on a fee-for-service basis and unfortunately we have a very poor collection rate. The other problem I would like to address has been brought up by the other discussants and that is the financial aspect. I have just finished reviewing the first 6 months of this year's hospital business office records, giving 3 months' collection time, and the collection rate has been only 30%. I would like to ask Dr. Boehm if the patients are more affluent in middle Tennessee or have better health insurance coverage? What has been their method of coping with this problem? Part of the reason for doing my study on the hospital financial deficit, and I am sure Dr. Boehm is doing the same thing, is to provide information for the next legislature in the hope of obtaining patient care dollars.

I commend this paper for its inherent quality and to each of you as an instruction guide in setting up a regional obstetrical program.

DR. CARL E. JOHNSON, Rochester, Minnesota. I would like to ask a question about legal liability in the case of a mother and child placed in an ambulance and transported 40 miles in a precarious situation. What is the medicolegal implication if the mother dies en route or the fetus dies in utero en route?

DR. A. WORK, JR., Ann Arbor, Michigan. I noticed that the majority of the patients were admitted for delivery. I would like to know the experience the authors have with those patients who were seen for consultation and then sent back undelivered to their community. What has been the response of the referring physicians in giving such patients follow-up after consultation in the case?

DR. ALFRED A. CARUSO, Kansas City, Missouri. In Kansas City in June, 1978, we added a helicopter service at a local hospital. Have you had any experience with transportation of mothers with helicopter or fixed-wing service?

DR. BOEHM (Closing). To begin with Dr. Nettle's question concerning the secret for obtaining legislative support, I think that there really are no secrets. It just takes perseverance.

The neonatologists in Tennessee were the prime movers originally. We as obstetricians and gynecologists need to become more involved locally in the political arena. Our Perinatal Advisory Committee has set up committees that look for legislative monies and we have certainly learned a great deal from reviewing the experience in other states and how they have obtained legislative money.

Currently, the legislature has deemed our obstetric regionalization program worth approximately half a million dollars and each of our regional centers receives an equal share.

None of this is patient care money but it does help pay for nurses and physicians, for some tests that are being performed in the tertiary center, and for other aspects of perinatal health care in the region.

The other point that needs to be raised is that when one approaches the legislature, it is important to emphasize certain interesting facts. For example, if one baby can be saved from institutionalization in the entire state, the state has been saved more than half a million dollars because that is what it costs for institutionalization of that particular individual. We are using this approach and it does seem to be working. I believe it is important to realize that we as physicians have to become involved in this political arena and not leave this important matter up to individuals who perhaps do not know as much about the medical field as we do.

Second, how cost effective is a Xerox Telecopier Network? We have recently reviewed our first 4 years' experience with the telecopier system and we did not address the cost effectiveness of this program. The important thing about the Telecopier Consultative Network is that it gives the private physician in a smaller community hospital a place to call when the tracing he or she is looking at is confusing. In the middle of the night nurses and doctors call our unit or my home and ask numerous important questions concerning the fetal monitor tracing. We often get into a lengthy discussion concerning the overall management of the case in question.

Concerning the problems that have occurred with shifting costs of those unable to pay, we have the same problems as expected in any other area. There is a certain write-off and someday there may come a limit as to how much money we can lose in the fetal intensive care unit. Hopefully upgrading insurance in the near future will help solve that problem. Money, as it relates to the regionalization program, will have to be a prime subject for all of us. I do know that the government is not necessarily the answer. The question in many ways lies with us.

Therefore, we in middle Tennessee have aggressively tried to do this work ourselves. We strongly believe that regionalization is a concept that is healthy and productive. It is what all of us want to do anyway, that is, to give good care, but we need to do it as a team and not as arrogant egotists who are trying to protect our little corner of the world. I believe that patients will respond favorably to this aspect of team care.

Dr. Stevenson commented about the military use and whether or not we have a Friday or Saturday or holiday "dump syndrome" at Vanderbilt. My response is that although my wife occasionally thinks that I am working harder on weekends than on other days, the fact is that this is not the case. We have witnessed a conscientious concern of family practitioners and obstetricians and gynecologists alike in sending patients whom they honestly believe can be better handled in our institution. It is a rare case where a physician sends a patient in merely to get that patient off his back because of the time of day or week.

Second, in regard to the question that concerned the primary physician's privileges at the tertiary center, there are no mechanisms for that at the present time. But, interestingly enough, in our travels around middle Tennessee, we asked physicians if they were interested in coming to Vanderbilt to continue the care at the tertiary center and most responded in a negative fashion, indicating that it would be very difficult for them to travel to Nashville to manage this. Obviously, in a regionalized system within a city, that may not be the case.

The other question of Dr. Stevenson concerned product and quality cost-benefit ratios. I do not think I have time to get into this aspect nor do I think that I could fully answer this very thoughtful question as I believe it is probably the bottom-line question for all of us. At the moment I have a hard time cost-effecting life. I know that sounds trite, but it still needs to be said.

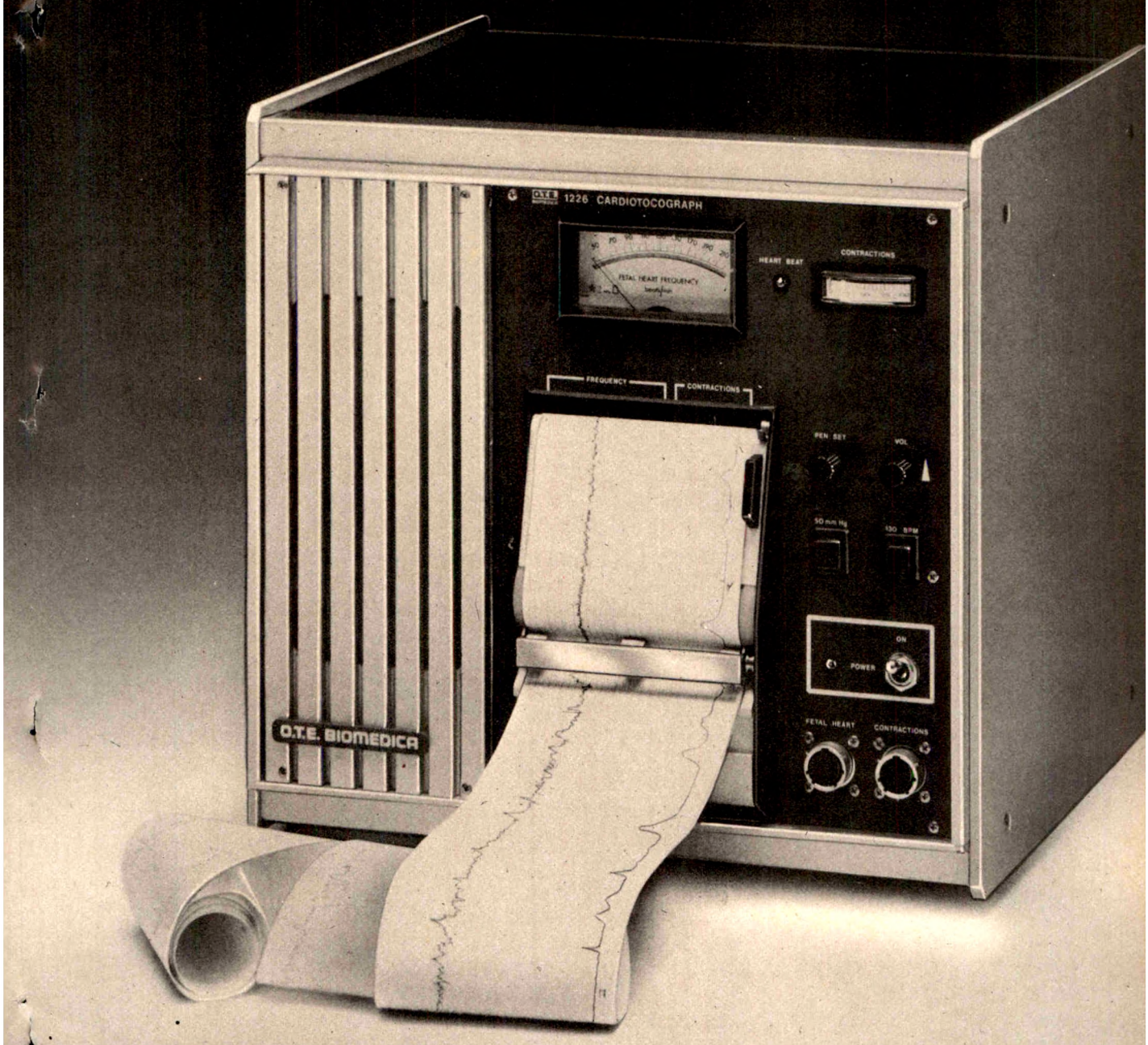
One hundred dollars a day in the hospital for a mother compared to perhaps a thousand dollars a day for the neonate sometimes can be proved to be cost effective. However, with couples wanting so desperately that happy, normal "product," as we all do, I have a hard time in cost-benefiting this type of system and I must admit that even if I did find that it was not cost effective, I do not think from what I have seen that I could stop this type of program.

Concerning Dr. King's comment about the type of patient who is sent in for maternal transport, it is interesting to note that the patients who are referred frequently have adequate coverage and it is not necessarily the indigent type of patient who is referred. In reviewing a number of patients recently, we noted that 16% had 100% coverage; 36% had 80% to 99% coverage; another 20% had 10% to 79% coverage, while only 28% had no coverage at all. Hopefully, these figures will look even better in the years ahead.

Concerning Dr. Johnson's question about legal liability and who is responsible when the mother is sent in and the mother or baby dies in route, my response is that the referring institution is responsible until the patient arrives at the tertiary center.

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While every precaution is taken to insure accuracy, we cannot guarantee against the possibility of an occasional change or omission in the preparation of this index.

Flagyl® (metronidazole) 250 mg.

Warning
Metronidazole has been shown to be carcinogenic in mice and possibly carcinogenic in rats. (See *Warnings*.) Unnecessary use of the drug should be avoided. Its use should be reserved for the conditions described in the *Indications* section.

Indications: For the treatment of symptomatic trichomoniasis in both females and males when the presence of the trichomonad has been confirmed by appropriate laboratory procedures (wet smears and/or cultures). Also for the treatment of asymptomatic females when the organism is associated with endocervicitis, cervicitis, or cervical erosion. *T. vaginalis* infection is a venereal disease and therefore, asymptomatic sexual partners of infected patients should be treated simultaneously if the organism is present. The decision to treat an asymptomatic male partner who has a negative culture or smear, or one in whom no culture has been attempted, is an individual one. In any event, the consort should be treated with Flagyl in cases of reinfection. Flagyl is also indicated for acute intestinal amebiasis (amebic dysentery) and for amebic liver abscess.

Contraindications: Evidence or history of blood dyscrasia, active organic disease of the CNS, the first trimester of pregnancy and a hypersensitivity to metronidazole.

Warnings: Flagyl should not be used in the first trimester of pregnancy (see *Contraindications*). Use with discretion during the second and third trimesters of pregnancy and restrict to those pregnant patients not cured by topical measures. Flagyl (metronidazole) is secreted in the breast milk of nursing mothers. It is not known whether this can be injurious to the newborn. If used during lactation, an alternative method of feeding may be elected.

Note: Tumorigenicity Studies in Rodents. Metronidazole has shown evidence of tumorigenic activity in a number of studies involving chronic, oral administration in mice and rats.

Most prominent among the effects in the mouse was the promotion of pulmonary tumorigenesis. This has been observed in all five reported studies in that species, including one study in which the animals were dosed on an intermittent schedule (administration during every fourth week only). The published results of one of the mouse studies indicate increases in the incidence of malignant lymphomas as well as pulmonary neoplasms associated with lifetime feeding of the drug. All these effects are statistically significant.

Two long-term toxicity studies in the rat have been completed. There was a statistically significant increase in the incidence of various neoplasms, particularly mammary tumors, among female rats administered metronidazole over that noted in the concurrent female control groups.

Two lifetime tumorigenicity studies in hamsters have been performed and reported to be negative.

Metronidazole has been reported to potentiate the anticoagulant effect of coumarin and warfarin resulting in a prolongation or prothrombin time. This possible drug interaction should be considered when Flagyl is prescribed for patients on this type of anticoagulant therapy.

Precautions: Mild leukopenia has been reported during Flagyl use; total and differential leukocyte counts are recommended before and after treatment with the drug, especially if a second course is necessary. Avoid alcoholic beverages during Flagyl therapy because abdominal cramps, nausea, vomiting, headaches and flushing may occur. Discontinue Flagyl promptly if abnormal neurologic signs occur. Exacerbation of moniliasis may occur. In amebic liver abscess, aspirate pus during metronidazole therapy.

Adverse Reactions: Nausea, headache, anorexia, vomiting, diarrhea, epigastric distress, abdominal cramping, constipation, a metallic, sharp and unpleasant taste, furry tongue, glossitis and stomatitis possibly associated with a sudden overgrowth of *Candida*, exacerbation of vaginal candidiasis, an occasional reversible moderate leukopenia, dizziness, incoordination and ataxia, numbness or paresthesia of an extremity, fleeting joint pains, confusion, irritability, depression, insomnia, mild erythematous eruptions, "weakness," urticaria, flushing, nasal congestion, dryness of the mouth, vagina or vulva, pruritus, dysuria, cystitis, a sense of pelvic pressure, dyspareunia, fever, polyuria, incontinence, decrease of libido, proctitis, pyuria and darkened urine have occurred in patients receiving the drug. Patients receiving Flagyl may experience abdominal distress, nausea, vomiting, flushing or headache if alcoholic beverages are consumed. The taste of alcoholic beverages may also be modified. Flattening of the T-wave may be seen in ECG tracings.

Dosage and Administration: ***For Trichomoniasis:*** The recommended dosage for both male and female is one 250-mg. tablet orally three times daily for seven days. When repeat courses of the drug are required, it is recommended that an interval of 4 to 6 weeks elapse between courses and that the presence of the trichomonad be reconfirmed by appropriate laboratory measures. Total and differential leukocyte counts should be made before, during and after retreatment. The male consort should be treated in any event in cases of reinfection.

For Amebiasis: *Adults:* For acute intestinal amebiasis, 750 mg. orally three times daily for 5 to 10 days.

For amebic liver abscess: *Adults:* 500 mg. or 750 mg. orally three times daily for 5 to 10 days.

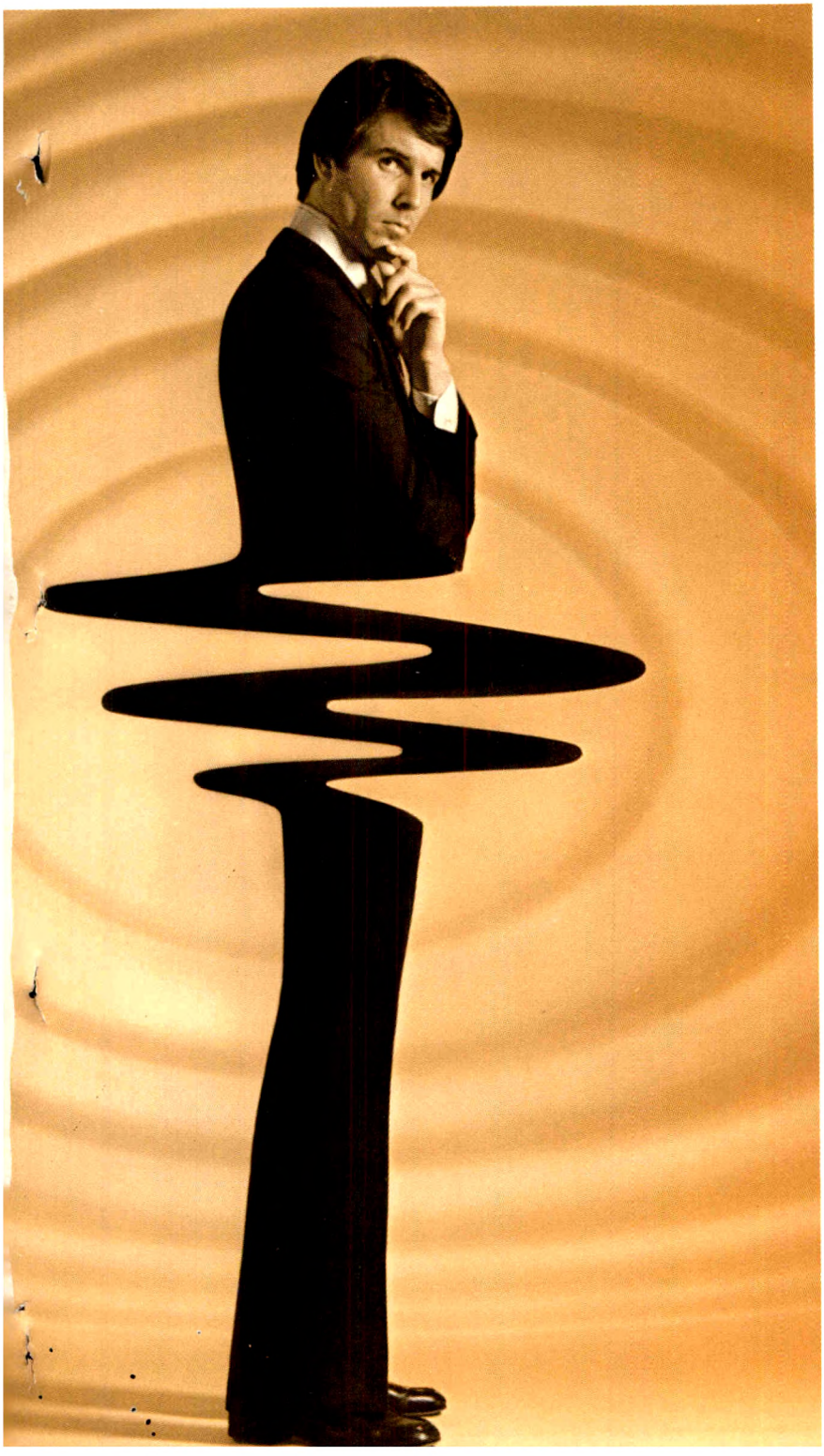
Children: 35 to 50 mg./kg. of body weight/24 hours, divided into three doses, orally for 10 days.

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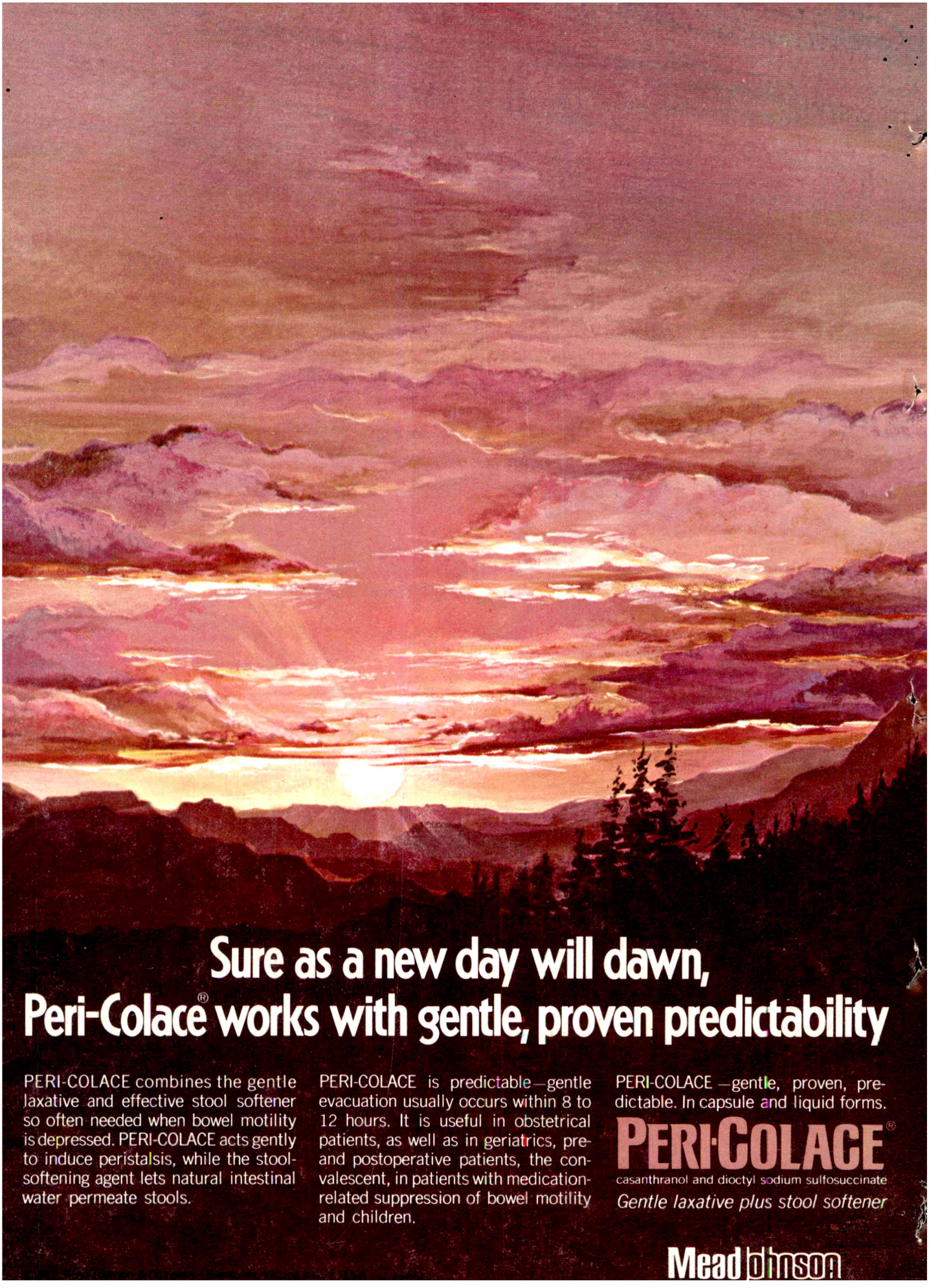
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The plight of today's teenager in these socially turbulent times is often precarious at best. According to a recent national survey, there has been a 30% increase in teenage sexual activity in the last five years.[1] Also, half of all out-of-wedlock births are attributed to teens. Up to two-thirds of these are unwanted, unplanned births.[2] Trapped in the midst of rapidly changing sexual mores, the teenager is further beset by uncertainty, timidity, ignorance, and misinformation.

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1. Zelnik, M. and Kantner, R.: Sexual and Contraceptive Experience of Young Married Women in the United States, 1976 and 1971. Family Planning Perspectives. Vol. 9, No. 2, March/April 1977.

2. Monthly Vital Statistics Report: Natality Statistics, National Center for Health Statistics, Vol. 26, No. 5, September 1977.

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CONTRAINDICATIONS 1. Known or suspected pregnancy (see Warning No. 5). 2. O.C.s should not be used in women who have or have had any of the following conditions: a. Thrombophlebitis or thromboembolic disorders. b. Cerebral vascular or coronary artery disease. c. Markedly impaired liver function. d. Known or suspected carcinoma of the breast. e. Known or suspected estrogen dependent neoplasia. f. Undiagnosed abnormal genital bleeding.

WARNINGS: Cigarette smoking increases the risk of serious cardiovascular side effects from O.C. use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use O.C.s should be strongly advised not to smoke.

The use of O.C.s is associated with increased risk of several serious conditions including thromboembolism, stroke, myocardial infarction, liver tumor, gall bladder disease, visual disturbances, fetal abnormalities, and hypertension. Practitioners prescribing O.C.s should be familiar with the following information relating to these risks.

1. *Thromboembolic Disorders and Other Vascular Problems:* An increased risk of thromboembolic and thrombotic disease associated with the use of O.C.s is well established. One British study demonstrated an increased relative risk for fatal venous thromboembolism; two British and three American studies demonstrated an increased relative risk for non-fatal venous thromboembolism. These studies estimate that users of O.C.s are 4 to 11 times more likely than nonusers to develop these diseases without evident cause. CEREBROVASCULAR DISORDERS. Two American studies demonstrated an increased relative risk for stroke, which had not been shown in prior British studies. In a collaborative American study of cerebrovascular disorders in women with and without predisposing causes, it was estimated that the relative risk of hemorrhagic stroke was 2.0 times greater in users than nonusers and the relative risk of thrombotic stroke was 4 to 9.5 times greater in users than in nonusers. A British long-term, follow-up study reported in 1976 a highly significant association between O.C. use and stroke. Another British long-term, follow-up study had suggested such an association in 1974, but the number of cases was too small to estimate the risk. MYOCARDIAL INFARCTION. An increased relative risk of myocardial infarction associated with the use of O.C.s has been reported, confirming a previously suspected association. One study conducted in the United Kingdom found, as expected, that the greater the number of underlying risk factors for coronary artery disease (cigarette smoking, hypertension, hypercholesterolemia, obesity, diabetes, history of preeclamptic toxemia) the higher the risk of developing myocardial infarction, regardless of whether the patient was an O.C. user or not. O.C.s, however, were found to be an additional risk factor. In terms of relative risk, it has been estimated that O.C. users who do not smoke (smoking is considered a major predisposing condition to myocardial infarction) are about twice as likely to have a fatal myocardial infarction as nonusers who do not smoke. O.C. users who are also smokers have about a 5-fold increased risk of fatal infarction compared to users who do not smoke, and about a 10- to 12-fold increased risk compared to nonusers who do not smoke. Furthermore, the number of cigarettes smoked is also an important factor. In determining the importance of these relative risks, however, the baseline rates for various age groups must be given serious consideration. (The estimates are based on British vital statistics which show acute myocardial infarction death rates 2- to 3-times less than in the U.S. for women in these age groups; consequently, actual U.S. death rates could be higher.) The importance of other predisposing conditions mentioned above in determining relative and absolute risks has not been quantified; other synergistic actions may exist. RISK OF DOSE. In an analysis of data derived from several national adverse reaction reporting systems, British investigators concluded that the risk of thromboembolism including coronary thrombosis is directly related to the dose of estrogen used in O.C.s. Preparations containing 0.1 mg or more of estrogen were associated with a higher risk of thromboembolism than those containing 0.05-0.08 mg of estrogen. Their analysis did suggest, however, that the quantity of estrogen may not be the sole factor involved. This finding has been supported by a study in the United States. Careful epidemiological studies to determine the degree of thromboembolic risk associated with progestogen-only O.C.s have not been performed. Cases of thromboembolic disease have been reported in women using these products, and they should not be presumed to be free of excess risk. ESTIMATE OF EXCESS MORTALITY FROM CIRCULATORY DISEASE. A large British prospective study estimated the mortality rate per 100,000 women per year from diseases of the circulatory system for users and nonusers of O.C.s according to age, smoking habits, and duration of use. The overall excess death rate annually from circulatory diseases for O.C. users was estimated to be 20 per 100,000 (ages 15-34—5/100,000; ages 35-44—33/100,000; ages 45-49—140/100,000). The risk is concentrated in older women, in those with a long duration of use, and in cigarette smokers, and may persist after discontinuation of O.C. use. It was not possible, however, to examine the interrelationships of age, smoking, and duration of use, nor to compare the effects of continuous vs. intermittent use. Although the study showed a 10-fold increase in death due to circulatory diseases in users for 5 or more years, all of these deaths occurred in women 35 or older. Until larger numbers of women under 35 with continuous use for 5 or more years are available, it is not possible to assess the magnitude of the relative risk for this younger age group. The available data from a variety of sources have been analyzed to estimate the risk of death associated with various methods of contraception. The estimates of risk of death for each method include the combined risk of the contraceptive method (e.g., thromboembolic and thrombotic disease in the case of O.C.s) plus the risk attributable to pregnancy or abortion in the event of method failure. This latter risk varies with the effectiveness of the contraceptive method. The findings of this analysis are shown in Table 1 below. The study concluded that the mortality associated with all methods of birth control is low and below that of childbirth, with the exception of O.C.s in women over 40 who smoke. (The rates given for pill only/smokers for each age group are for smokers as a class. For "heavy" smokers (more than 15 cigarettes a day), the rates given would be about double; for "light" smokers (less than 15 cigarettes a day), about 50 percent.) The lowest mortality is associated with the condom or diaphragm backed up by early abortion. The study also concluded that O.C. users who smoke, especially those over the age of 30, have a greater mortality risk than O.C. users who do not smoke.

TABLE 1. *The annual number of deaths associated with control of fertility and no control per 100,000 nonsterile women by regimen of control and age of women are:*

	15-19	20-24	25-29	30-34	35-39	40-44
No method	5.6	6.1	7.4	13.9	20.8	22.6
Abortion only	1.2	1.6	1.8	1.7	1.9	1.2
Pill only—nonsmokers	1.3	1.4	1.4	2.2	4.5	7.1
Pill only—smokers	1.5	1.6	1.6	10.8	13.4	58.9
IUDs only	0.9	1.0	1.2	1.4	2.0	1.9
Traditional contraception only	1.1	1.6	2.0	3.6	5.0	4.2
Traditional contraception and abortion	0.2	0.2	0.3	0.3	0.3	0.2

The risk of thromboembolic and thrombotic disease associated with O.C.s increases with age after approximately age 30 and, for myocardial infarction, is further increased by hypertension, hyperlipidemias, obesity, diabetes, or history of preeclampic toxemia and especially by cigarette smoking. Based on the data currently available, the following table gives a gross estimate of the risk of death from circulatory disorders associated with the use of O.C.s:

TABLE 2. *Smoking habits and other predisposing conditions – risk associated with use of O.C.s*

Age	Below 30	30-39	40+
Heavy smokers	C	B	A
Light smokers	D	C	B
Nonsmokers (No predisposing conditions)	D	C,D	C
Nonsmokers (other predisposing conditions)	C	C,B	B,A

A—Use associated with very high risk. C—Use associated with moderate risk.
B—Use associated with high risk. D—Use associated with low risk.

The physician and the patient should be alert to the earliest manifestations of thromboembolic and thrombotic disorders (e.g., thrombophlebitis, pulmonary embolism, cerebrovascular insufficiency, coronary occlusion, retinal thrombosis, and mesenteric thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately. A four- to six-fold increased risk of post-surgery thromboembolic complications has been reported in O.C. users. If feasible, O.C.s should be discontinued at least 4 weeks before surgery of a type associated with an increased risk of thromboembolism or prolonged immobilization. Among patients with thromboembolic disease, the results of retrospective studies suggest the possibility of an increased risk for users who are of blood types A, B, or AB, as compared with those of type O. *Ocular Lesions:* There have been reports of neuro-ocular lesions such as optic neuritis or retinal thrombosis associated with the use of O.C.s. Discontinue O.C. medication if there is unexplained, sudden or gradual, partial or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal vascular lesions; and institute appropriate diagnostic and therapeutic measures. *Carcinoma:* Long-term continuous administration of either natural or synthetic estrogen in certain animal species increases the frequency of certain adenomas, benign or malignant, such as those of the breast, cervix, vagina, uterus, ovary, pituitary and liver. Certain synthetic progestogens, none currently contained in O.C.s, have been noted to increase the incidence of mammary nodules, benign and malignant, in dogs. Several retrospective case-control studies have reported an increased relative risk (3.1 to 13.9 times) associating endometrial carcinoma with the prolonged use of estrogens in postmenopausal women who took estrogen replacement medication to relieve menopausal symptoms. One publication reported on the first 30 cases submitted by physicians to a registry of cases of adenocarcinoma of the endometrium in women under 40 on O.C.s. Of the adenocarcinomas found in women without predisposing risk factors for adenocarcinoma of the endometrium (e.g., irregular bleeding at the time O.C.s were first given, polycystic ovaries) nearly all occurred in women who had used a sequential O.C. These products are no longer marketed. No statistical association has been reported suggesting an increased risk of endometrial cancer in users of conventional combination or progestogen-only O.C.s, although individual cases have been reported. Several studies have shown no increased risk of breast cancer to women taking O.C.s or estrogens. In one study, however, while no overall increased risk of breast cancer was noted in women treated with O.C.s, a greater risk was suggested for the subgroups of O.C. users with documented benign breast disease and for long-term (2-4 years) users. One other study indicated an increasing risk of breast cancer in women taking menopausal estrogens, which increased with duration of follow-up. A reduced occurrence of benign breast tumors in users of O.C.s has been well documented. In a prospective study of women with cervical dysplasia, there was an increase in severity and of conversion to cancer *in situ* in O.C. users compared with nonusers. This became statistically significant after 3 to 4 years of use. Nonreversal of dysplasia within the first 6 months of pill use was suggested to be predictive of progression after prolonged exposure. There have been other reports of microglandular hyperplasia of the cervix in users of O.C.s. In summary, there is at present no confirmed evidence from human studies of an increased risk of cancer associated with O.C.s. Close clinical surveillance of all women taking O.C.s is, nevertheless, essential. In all cases of undiagnosed persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be taken to rule out malignancy. Women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease or abnormal mammograms should be monitored with particular care if they elect to use O.C.s instead of other methods of contraception. 4. *Liver Tumors:* Sudden severe abdominal pain or shock may be due to rupture and hemorrhage of a liver tumor. There have been reports associating benign or malignant liver tumors with O.C. use. This has been reported in short-term as well as long-term users of O.C.s. One study showed that O.C. formulations with high hormonal potency were associated with a higher risk than lower potency formulations. Two studies relate risk with duration of use, the risk being much greater after 4 or more years of use. Although it is an uncommon lesion, it should be considered in women presenting with an "acute abdomen". The tumor may cause serious or fatal hemorrhage. Patients with liver tumors have demonstrated variable clinical features which may make preoperative diagnosis difficult. Some cases presented because of right upper quadrant masses, while most had signs and symptoms of acute intraperitoneal hemorrhage. Routine radiological and laboratory studies may not be helpful. Liver scans may clearly show a focal defect. Hepatic arteriography may be a useful procedure in diagnosing primary liver neoplasm. 5. *Use in or Immediately Preceding Pregnancy, Birth Defects in Offspring, and Malignancy in Female Offspring:* The use of female sex hormones—both estrogenic and progestational agents—during early pregnancy may seriously damage the offspring. It has been shown that females exposed *in utero* to diethylstilbestrol, a nonsteroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare. This risk has been estimated to be of the order of 1 in 1,000 exposures or less. Although there is no evidence at the present time that O.C.s further enhance the risk of developing this type of malignancy, such patients should be monitored with particular care if they elect to use O.C.s instead of other methods of contraception. Furthermore, a high percentage of women exposed to diethylstilbestrol (from 30 to 90%) have been found to have epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether this condition is a precursor of vaginal malignancy. Male children so exposed may develop abnormalities of the urogenital tract. Although similar data are not available with the use of other estrogens, it cannot be presumed that they would not induce similar changes. An increased risk of congenital anomalies, including heart defects and limb defects, has been reported following use of sex hormones, including O.C.s, in pregnancy. In one case-control study it was estimated that there was a 4.7-fold increased relative risk of limb-reduction defects in infants exposed *in utero* to sex hormones (O.C.s, hormonal withdrawal tests for pregnancy or attempted treatment for threatened abortion). Some of these exposures were very short and involved only a few days of treatment. The data suggest that the risk of limb-reduction defects in exposed fetuses is somewhat less than 1 in 1,000 live births. In a large prospective study, cardiovascular defects in children born to women who received female hormones, including O.C.s, during early pregnancy occurred at a rate of 18.2 per 1,000 births, compared to 7.8 per 1,000 for children not so exposed *in utero*. These results are statistically significant. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well controlled studies that progestogens are effective for these uses. There is some evidence that triploidy and possibly other types of polyploidy are increased among abortuses from women who become pregnant soon after ceasing O.C.s. Embryos with these anomalies are virtually always aborted spontaneously. Whether there is an overall increase in spontaneous abortion of pregnancies conceived soon after stopping O.C.s is unknown. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at the time of the first missed period (or after 45 days from the last menstrual period if progestogen-only O.C.s are used) and further use of O.C.s should be withheld until pregnancy has been ruled out. It is recommended that for any patient who has missed two consecutive periods, pregnancy should be ruled out before continuing the contraceptive regimen. If pregnancy is confirmed, the patient should be apprised of the potential risks to the fetus and the advisability of continuation of the pregnancy should be discussed in the light of these risks. It is also recommended that women who discontinue O.C.s with the intent of becoming pregnant use an alternate form of contraception for a period of time before attempting to conceive. Many clinicians recommend 3 months, although no precise information is available [illegible]

mendation. The administration of progestogen-only or progestogen-estrogen combinations to induce withdrawal bleeding should not be used as a test of pregnancy. 6. *Gall Bladder Disease:* Studies report an increased risk of gall bladder disease in users of O.C.s or estrogens. In one study, an increased risk appeared after 2 years of use and doubled after 4 or 5 years of use. In another study an increased risk was apparent between 6 and 12 months of use. 7. *Carbohydrate and Lipid Metabolic Effects:* A decrease in glucose tolerance has been observed in a significant percentage of patients on O.C.s. For this reason, prediabetic and diabetic patients should be carefully observed while receiving O.C.s. An increase in triglycerides and total phospholipids has been observed in patients receiving O.C.s. The clinical significance of this finding is unknown. 8. *Elevated Blood Pressure:* An increase in blood pressure has been reported with O.C. use. In some women, hypertension may occur within a few months of beginning O.C. use. In the first year of use, the prevalence of women with hypertension is low in users and may be no higher than that of a comparable group of nonusers. The prevalence in users increases, however, with longer exposure, and in the fifth year of use is two and a half to three times the reported prevalence in the first year. Age is also strongly correlated with the development of hypertension in O.C. users. Women with a history of elevated blood pressure (hypertension), preexisting renal disease, a history of toxemia or elevated blood pressure during pregnancy, a familial tendency to hypertension or its consequences, or a history of excessive weight gain or fluid retention during the menstrual cycle may be more likely to develop elevation of blood pressure when given O.C.s and, therefore, should be monitored closely. Even though elevated blood pressure may remain within the "normal" range, the clinical implications of elevations should not be ignored and close surveillance is indicated, particularly for women with other risk factors for cardiovascular disease or stroke. High blood pressure may or may not persist after discontinuation of the O.C. 9. *Headache:* The onset or exacerbation of migraine or development of headache of a new pattern which is recurrent, persistent, or severe, requires discontinuation of O.C.s and evaluation of the cause. 10. *Bleeding Irregularities:* Breakthrough bleeding, spotting, and missed menses are frequent reasons for patients discontinuing O.C.s. In breakthrough bleeding, as in all cases of irregular bleeding from the vagina, nonfunctional causes should be borne in mind. In undiagnosed persistent or recurrent abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy. If pathology has been excluded, time or a change to another formulation may solve the problem. Changing to an O.C. with a higher estrogen content, while potentially useful in minimizing menstrual irregularity, should be done only if necessary since this may increase the risk of thromboembolic disease. Women with a past history of oligomenorrhea or secondary amenorrhea or young women without regular cycles may have a tendency to remain anovulatory or to become amenorrheic after discontinuation of O.C.s. Women with these preexisting problems should be advised of this possibility and encouraged to use other contraceptive methods. Post-use anovulation, possibly prolonged, may also occur in women without previous irregularities. A higher incidence of galactorrhea and of pituitary tumors (e.g., adenomas) has been associated with amenorrhea in former users compared with nonusers. One study reported a 16-fold increased prevalence of pituitary prolactin-secreting tumors among patients with postpill amenorrhea when galactorrhea was present. 11. *Infertility:* There is evidence of impairment of fertility in women discontinuing O.C.s in comparison with those discontinuing other methods of contraception. The impairment appears to be independent of the duration of use of the preparations. While the impairment diminishes with time, there is still an appreciable difference in the results in nulliparous women for the O.C. and non-O.C. groups 30 months after discontinuation of birth control. For parous women the difference is no longer apparent 30 months after cessation of contraception. 12. *Ectopic Pregnancy:* Ectopic as well as intrauterine pregnancy may occur in contraceptive failures. However, in progestogen-only O.C. failures, the ratio of ectopic to intrauterine pregnancies is higher than in women who are not receiving O.C.s, since the drugs are more effective in preventing intrauterine than ectopic pregnancies. 13. *Breast Feeding:* O.C.s given in the postpartum period may interfere with lactation. There may be a decrease in the quantity and quality of the breast milk. Furthermore, a small fraction of the hormonal agents in O.C.s has been identified in the milk of mothers receiving these drugs. The effects, if any, on the breast fed child have not been determined. If feasible, the use of O.C.s should be deferred until the infant has been weaned. **PRECAUTIONS** *GENERAL* 1. A complete medical and family history should be taken prior to the initiation of O.C.s. The pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen and pelvic organs, including Papanicolaou smear and relevant laboratory tests. As a general rule, O.C.s should not be prescribed for longer than 1 year without another physical examination being performed. 2. Under the influence of estrogen-progestogen preparations, preexisting uterine leiomyomata may increase in size. 3. Patients with a history of psychic depression should be carefully observed and the drug discontinued if depression recurs to a serious degree. Patients becoming significantly depressed while taking O.C.s should stop the medication and use an alternate method of contraception in an attempt to determine whether the symptom is drug related. 4. O.C.s may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention, such as convulsive disorders, migraine syndrome, asthma or cardiac, hepatic or renal insufficiency. 5. Patients with a past history of jaundice during pregnancy have an increased risk of recurrence of jaundice while receiving O.C. therapy. If jaundice develops in any patient receiving such drugs, the medication should be discontinued. 6. Steroid hormones may be poorly metabolized in patients with impaired liver function and should be administered with caution in such patients. 7. O.C. users may have disturbances in normal tryptophan metabolism which may result in a relative pyridoxine deficiency. The clinical significance of this is unknown. 8. Serum folate levels may be depressed by O.C. therapy. Since the pregnant woman is predisposed to the development of folate deficiency and the incidence of folate deficiency increases with increasing gestation, it is possible that if a woman becomes pregnant shortly after stopping O.C.s, she may have a greater chance of developing folate deficiency and complications attributed to this deficiency. 9. The pathologist should be advised of O.C. therapy when relevant specimens are submitted. 10. Certain endocrine and liver function tests and blood components may be affected by estrogen-containing O.C.s. For example: a. Increased sulfobromophthalein retention. b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability. c. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered. d. Decreased pregnanediol excretion. e. Reduced response to metyrapone test. *DRUG INTERACTIONS* O.C.s may be rendered less effective by virtue of drug interaction with rifampin, isoniazid, ampicillin, neomycin, penicillin V, chloramphenicol, sulfonamides, nitrofurantoin, barbiturates, phenytoin, primidone, analgesics, tranquilizers and antimigraine preparations. O.C.s may alter the effectiveness of other types of drugs, such as oral anticoagulants, anticonvulsants, tricyclic antidepressants, antihypertensive agents (e.g., quanethidine), vitamins and hypoglycemic agents. *CARCINOGENESIS* See Warnings. *PREGNANCY* Pregnancy category X. See Contraindications and Warnings. *NURSING MOTHERS* See Warnings. **ADVERSE REACTIONS** An increased risk of the following serious adverse reactions has been associated with the use of O.C.s (see Warnings): thrombophlebitis, thrombosis, pulmonary embolism, coronary thrombosis, cerebral thrombosis, mesenteric thrombosis, liver tumors, cerebral hemorrhage, hypertension, gall bladder disease, congenital anomalies, neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis. The following adverse reactions have been reported in patients receiving O.C.s and are believed to be drug related: bleeding irregularities (breakthrough bleeding, spotting, missed menses during treatment, amenorrhea after treatment), gastrointestinal symptoms (nausea, vomiting, bloating, abdominal cramps), dysmenorrhea, infertility after discontinuance of treatment, edema, chloasma or melasma which may persist after drug is discontinued, breast changes (tenderness, enlargement, and secretion), intolerance to contact lenses, change in corneal curvature (steepening) change in weight (increase or decrease), change in cervical erosion and cervical secretion, possible diminution in lactation when given immediately postpartum, cholestatic jaundice, migraine, increase in size of uterine leiomyomata, rash (allergic), mental depression, reduced tolerance to carbohydrates, vaginal candidiasis, prolactin-secreting pituitary tumors. The following adverse reactions have been reported in users of O.C.s, and the association has been neither confirmed nor refuted: premenstrual-like syndrome, cataracts, changes in libido, chorea, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, hirsutism, loss of hair, erythema multiforme, erythema nodosum, hemorrhagic eruption, vaginitis, porphyria, impaired renal function.

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Reanastomosis of the fallopian tube (ampullary-ampullary)

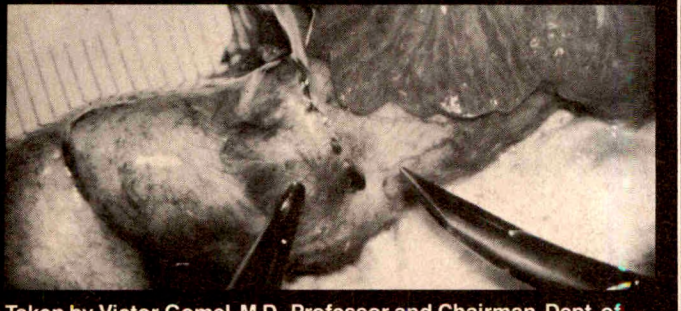
a. Hemostasis is obtained by bipolar microforceps.



b. Placement of suture to the muscular layer.



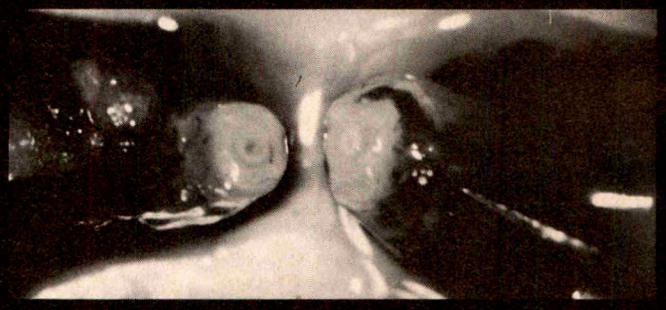
c. The anastomosis is completed by the approximation of the serosa.



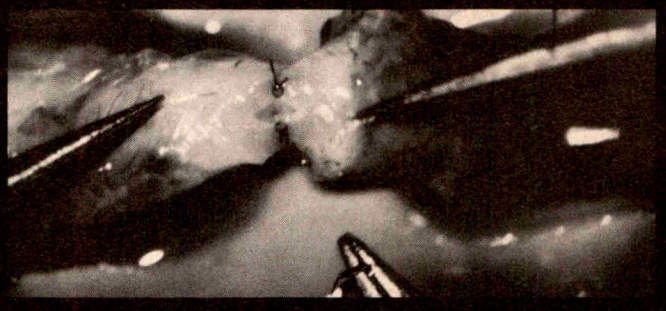
Taken by Victor Gomel, M.D., Professor and Chairman, Dept. of Obstetrics and Gynaecology, University of British Columbia, Vancouver.

Reanastomosis of the vas deferens

a. Before



b. During placement of suture.



c. Placement of suture in epididymal tube.



Taken by Sherman J. Silber, M.D., Dept. of Urology and Microsurgery, St. Luke West Hospital, St. Louis, Missouri.

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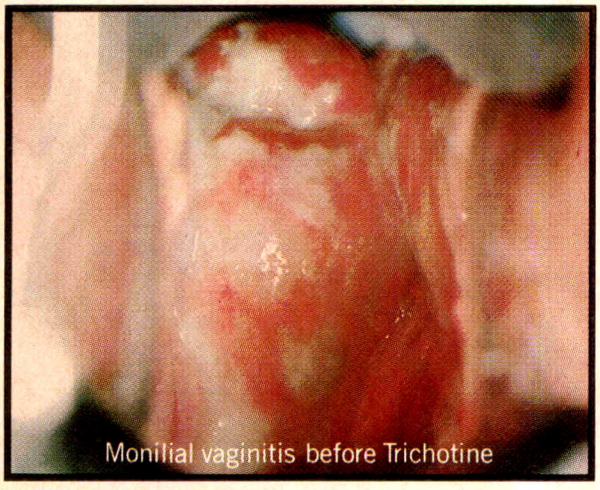
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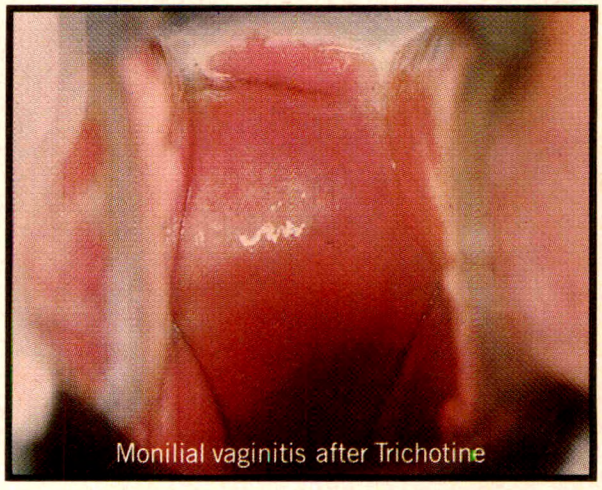
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You're looking at the only medical reason to recommend a douche.



Monilial vaginitis before Trichotine



Monilial vaginitis after Trichotine

When douching can enhance therapy of vaginitis, as in the photographs above, it has a definite place in medicine. And such evidence, as described by numerous clinical investigators over the years, is exactly the reason Trichotine® receives extensive professional recommendation.

By clearing away obstructive vaginal discharge, Trichotine affords better access to infected mucosa during topical vaginitis therapy and speeds symptomatic relief when used with systemic agents.

One investigator, for example, found that "relief of itching and leukorrhea is prompt and enhances the results obtained with the specific therapy."[1] In subsequent studies[2,3] of patients with vaginitis, others have confirmed this rapid symptomatic relief.

Further, following surgical procedures such as cervical cryosurgery, douching with Trichotine has "...proved to be an effective adjunct in...reducing vaginal discharge, irritation, discomfort and patient complaints."[4] Similar benefits were reported in cervical cauterization,[5] in acute inflammatory[6] and chronic pelvic disease.[7]

Cleanses better than acid douches/Works differently than iodophor douches.

Alkalinity enhances the detergent action of Trichotine—by lowering surface tension and increasing mucolytic action. This results in more thorough vaginal cleansing than with acid douches.[8,9] And, unlike acid douches, Trichotine won't coagulate and precipitate vaginal debris.[8] Or burn as acid douches tend to do.

Unlike iodophor douches, Trichotine doesn't upset the vaginal flora by introducing broad-spectrum antimicrobials. Its actions are limited to those you expect from an adjunctive douche: mucolytic, antipruritic, detergent and deodorizing.

Trichotine: The more you know about it, the more professional reasons you have to recommend douching.

References:

1. Glynn, R.: *Med. Times* 96:170, Feb. 1968. 2. Gotlib, M.H. and Adler, D.N.: *Med. Times* 96:902, Sept. 1968. 3. Cohen, R.S., *et al.*: *Curr. Ther. Res.* 15:11, Nov. 1973. 4. Laubach, G.E. and Wilchins, S.A.: *Cancer Cytology* 13:10, July-Dec. 1973. 5. Novak, E.R., Jones, G.S. and Jones, H.W.: *Novak's Textbook of Gynecology*, ed. 8. Baltimore, The Williams & Wilkins Company, 1970. p. 203. 6. *Ibid.*, p. 356. 7. *Ibid.*, p. 366. 8. Glynn, R.: *Obstet. Gynecol.* 22:640, Nov. 1963. 9. Fischer, R.R.: *Pacif. Med. Surg.* 73:209, May-June 1965.

POWDER/LIQUID DISPOSABLE **Trichotine®** VAGINAL DOUCHE

The gynecologic adjunct.

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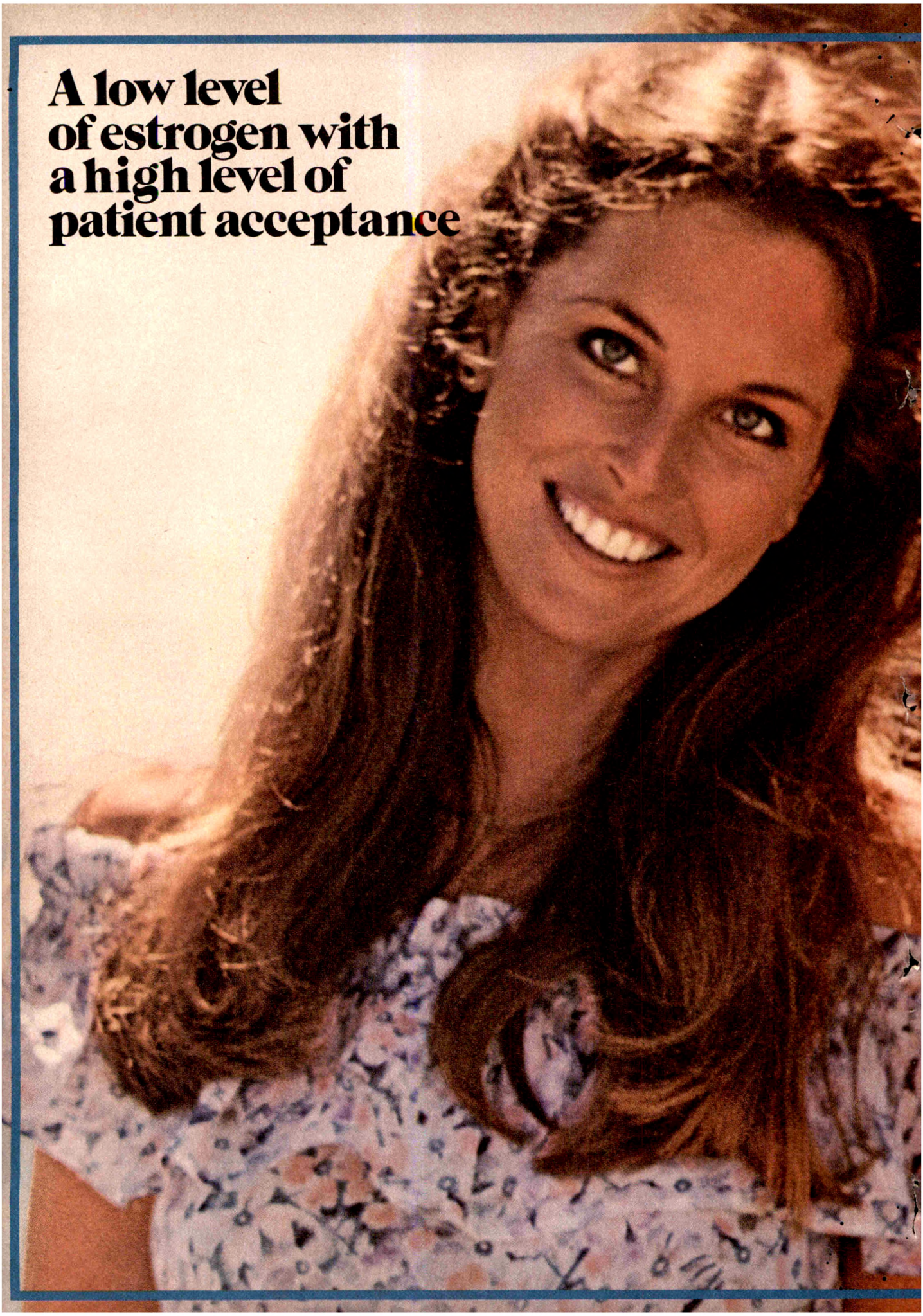
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A low level
of estrogen with
a high level of
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"In deciding which combination drug to initially prescribe it is best to utilize the combination pill with the lowest effective dose and an acceptable level of side effects."

Mishell, D.: Current Status of Oral Contraceptive Steroids, Clin. Obstet. Gynecol. *19*:743-764 (December) 1976.

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Discontinuation (cumulative) per 100 woman-years of use	0.7	1.1	2.0	3.0	3.5	4.2

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Serious as well as minor side effects have been reported with the use of oral contraceptives. These include thromboembolic disease. The physician should remain alert to the earliest manifestations of any symptoms of serious disease or conditions and discontinue oral contraceptive therapy when appropriate. The physician should be fully familiar with the complete prescribing information for this product.

SEARLE

Indication and usage—For prevention of pregnancy. Pregnancy rate using products with ≥35 mcg. ethinyl estradiol or ≥50 mcg. mestranol is <1/100 woman-years. With ≤35 mcg. ethinyl estradiol, rate is slightly higher; with progestogen-only oral contraceptives (OCs), rate is about 3. Precise comparisons cannot be made. Rates for other methods have been published. Dose-related Thromboembolic Risk—One study showed positive association between OC estrogen dose and thromboembolic risk. Thus, it is prudent and in keeping with good therapeutics to minimize estrogen exposure. Prescribe product containing the least amount of estrogen compatible with acceptable pregnancy rate and patient acceptance. Start new OC users on ≤50 mcg. estrogen.

Contraindications—Thrombophlebitis, thromboembolic disorders, cerebral vascular disease, myocardial infarction or coronary artery disease, or past history of these; known or suspected breast carcinoma, estrogen-dependent neoplasia, or pregnancy; undiagnosed abnormal vaginal bleeding; markedly impaired liver function; past or present, benign or malignant liver tumors.

Warnings

Cigarette-smoking increases risk of serious cardiovascular side effects from OC use. Risk increases with age and heavy smoking (15 or more cigarettes/day) and is quite marked in women over 35. OC users should be strongly advised not to smoke.

OCs are associated with increased risk of several serious conditions including venous and arterial thromboembolism, thrombotic and hemorrhagic stroke, myocardial infarction, visual disorders, hepatic tumors, gallbladder disease, hypertension, fetal abnormalities. Practitioners should be familiar with the available information relating to these and other risks.

1. Thromboembolic disorders and other vascular problems—Increased risk of thromboembolic and thrombotic disease associated with OCs is well established. A British study showed increased relative risk for fatal venous thromboembolism, 2 British and 3 U.S. studies increased relative risk for nonfatal venous thromboembolism. Two U.S. studies showed increased relative risk for stroke, not shown in prior British studies. It was estimated OC users were 2–11 times more likely than nonusers to manifest these diseases without evident cause. In a British study of idiopathic deep vein thrombosis and pulmonary embolism, projected hospitalization rates for ages 16-40 were 47/year/100,000 users and 5 for nonusers. In a British mortality study, overall excess mortality from pulmonary embolism or stroke was 1.3–3.4 deaths/year/100,000 users and increased with age. Cerebrovascular Disorders—In a U.S. study of stroke with and without predisposing causes, risk of hemorrhagic stroke was estimated as 2 times greater and thrombotic stroke 4.0–9.5 times greater in users. Mortality trends in 21 countries indicate that, since OC introduction, changes in mortality from nonrheumatic cardiovascular disease were associated with changes in the prevalence of OC use. The Royal College of GPs reported on its prospective study comparing users and nonusers: "A statistically significant higher rate of reporting of cerebrovascular accidents in Takers is evident, but the numbers are too small to justify an estimation of the degree of risk." They reported more superficial and deep vein thrombosis in users. A 1977 analysis showed a 5-fold increased mortality in users from circulatory diseases, mainly myocardial infarction (MI) and hemorrhagic stroke. Excess mortality was associated with age, smoking and duration of use. In 1976 a British Family Planning Association study found a highly significant association between OC use and stroke though total numbers were small; the increased risk for venous thrombosis and pulmonary embolism was about 4-fold and statistically highly significant. Circulatory disease mortality was significantly greater in users. Myocardial Infarction—An increased risk of MI associated with OC use was reported in Britain, as previously suspected. The morbidity study found the greater the number of risk factors for coronary artery disease (smoking, hypertension, hypercholesterolemia, obesity, diabetes, history of pre-eclamptic toxemia) the higher the MI risk, regardless of OC use. OCs were considered an additional risk factor. The excess rate of fatal MI in Britain was about 3.5/year/100,000 users aged 30–39 and 20 for ages 40–44. (These are based on British vital statistics with acute MI death rates 2–3 times less than the U.S. Similar estimates for U.S. are 25.7 for users aged 30–39 with predispositions vs. 1.5 without; for ages 40–44, 86.2 vs. 5.1.) Excess hospitalization rate for nonfatal MI in Britain was about 3.5/year/100,000 users aged 30–39 and 47 for ages 40–44. Smoking is a major predisposing condition to MI. In terms of relative risk, nonsmoking OC users are twice as likely to have fatal MI as nonsmoking nonusers. Smoking users have a 5-fold greater risk of fatal MI as nonsmoking users, but a 10–12-fold greater risk than nonsmoking nonusers. Amount of smoking is an important factor. In determining importance of these risks, give serious consideration to rates in table below. Importance of other predispositions cited above in determining relative and absolute risks has not been quantified; it is likely the same synergism exists, but perhaps to a lesser extent.

Estimated Mortality Rate from Myocardial Infarction per 100,000 Women/Year

	Aged 30–39		Aged 40–44	
	Users	Nonusers	Users	Nonusers
All smokers	10.2	2.6	62.0	15.9
≥15 cigarettes daily	13.0	5.1	78.7	31.3
<15 cigarettes daily	4.7	0.9	28.6	5.7
Nonsmokers	1.8	1.2	10.7	7.4
Smokers and nonsmokers	5.4	1.9	32.8	11.7

Risk of Dose—Reports of thromboembolism after use of OCs with ≥50 mcg. estrogen received by drug safety committees in Britain, Sweden and Denmark were compared with the distribution expected from market research sales estimates. A positive correlation was found between estrogen dose and reporting of thromboembolism, including coronary thrombosis, in excess of that predicted by sales. OCs with ≥100 mcg. estrogen were associated with higher thromboembolism risk than those with 50–80 mcg. The authors suggested that estrogen quantity may not be the sole factor. Any influence of progestogens was not considered, which may be responsible for certain discrepancies in the data. No significant differences were noted between OCs containing the same estrogen dose nor between ethinyl estradiol and mestranol. Studies on thromboembolic risk with progestogen-only OCs have not been done. Cases have been reported for these OCs and they are not presumed free of excess risk. In a U.S. case-controlled study, relative risk of OC use 1 month before hospitalization for various types of thromboembolism was calculated. If relative estrogenic potency and possible influence of different progestogens are ignored, OCs may be divided into those with <100 mcg. and those with ≥100 mcg. estrogen. For all cases combined, larger doses were associated with only slightly higher relative risk; for idiopathic cases relative risk was doubled with larger doses, but confidence limits overlapped and differences were not significant. Apparently there was no increased risk for cases with predispositions. Thromboembolic risk in users and nonusers increases with age. OCs have been considered an independent risk factor. Excess Mortality from Circulatory Diseases—A U.K. prospective study estimated annual mortality from circulatory diseases for OC users and nonusers according to age, smoking habits and duration of use. Excess mortality was 20/100,000 users (5 for ages 15–34, 33 for ages 35–44, 140 for ages 45–49), the risk being concentrated in older women, long-term users, and smokers. Interrelationships of age, smoking and duration of use could not be examined, nor could effects of continuous vs. intermittent use. Though circulatory mortality was increased 10-fold in users of >5 years, all deaths were in women over age 34. Until more under-35 users of 5+ continuous years are available, size of relative risk for this age group cannot be given. Risk of circulatory disease may have persisted after discontinuance of OCs. One study estimated risk of death with various contraceptive methods, each estimate including risk of method (e.g., thromboembolism for OCs) plus risk due to pregnancy or abortion in cases of method failure. This latter risk varies with effectiveness. It concluded mortality with all methods is low and below that of childbirth, except for OC users over 40 who smoke. Heavy smokers have double the risk of smokers as a class, light smokers about half. Mortality associated with OC use in nonsmokers over 40 is higher than with any other method in that age group. Lowest mortality is with the condom or diaphragm backed up by early legal abortion. Risk of thromboembolic and thrombotic disease associated with OCs increases with age after 30 and, for MI, is further increased by hypertension, hypercholesterolemia, obesity, diabetes, history of pre-eclamptic toxemia, and especially cigarette smoking. Based on current data, the chart gives gross estimates of risk of death from circulatory disorders associated with OCs:

Risk is: A—very high, B—high, C—moderate, D—low. Age:	<30	30–39	≥40
Heavy smokers (≥15/day)	C	B	A
Light smokers (<15/day)	D	C	B
Nonsmokers, no predispositions	D	C,D	C
Nonsmokers, with predispositions	C	C,B	B,A

Physician and patient should be alert to earliest manifestations of thromboembolic and thrombotic disorders (e.g., thrombophlebitis, pulmonary embolism, cerebrovascular insufficiency, coronary artery disease, myocardial infarction, retinal thrombosis, mesenteric thrombosis). Should any of these occur or be suspected, discontinue OCs immediately. A 4–7-fold increased risk of postsurgery thromboembolism was reported in users; if feasible discontinue OCs at least 4 weeks before elective surgery or during prolonged immobilization and do not resume until at least 4 weeks postsurgery. Thromboembolic risk may be increased for users with blood types A, B or AB. **2.** Ocular lesions—Neuro-ocular lesions such as optic neuritis or retinal thrombosis have been associated with OCs. Discontinue if there is unexplained, gradual or sudden, partial or complete loss of vision; proptosis or diplopia; papilledema; or evidence of retinal vascular lesions. Institute diagnostic and therapeutic measures. **3.** Carcinoma—Long-term estrogen in certain animals increases carcinomas such as those of breast, uterus, cervix, vagina, ovary, liver, pituitary. Some synthetic progestogens, none currently in OCs, increase incidence of benign and malignant mammary nodules in dogs. There is now evidence that estrogens increase risk of human endometrial carcinoma. In several case-controlled studies increased relative risk (3.1–13.9 times) associated endometrial carcinoma with prolonged estrogen for menopausal symptoms. Risk was independent of other known risk factors and depended on duration of use and dose. This is supported by increased endometrial cancer incidence since 1969 in 8 U.S. areas with cancer-reporting systems, which may be related to rapidly expanding estrogen use. There is no evidence that natural estrogens are more or less hazardous than synthetics at equi-estrogenic doses. Of the first 30 cases of endometrial carcinoma in OC users under 40, those without predispositions (e.g., irregular bleeding before OCs, polycystic ovaries) occurred nearly always with no-longer-marketed sequential OCs. No statistical association is reported suggesting increased endometrial cancer with combination or progestogen-only OCs, though individual cases have been reported. Studies show no increased breast cancer with OCs or estrogens. However, greater risk was noted in OC users with benign breast disease or long-term (2–4 years) use. Risk of breast cancer with menopausal estrogens rose and further increased with duration of follow-up. Decreased benign breast tumors in OC users is well known. Some studies suggested increased risk of cervical dysplasia, erosion and carcinoma in long-term users; cause and effect is not established. Cervical microglandular hyperplasia has been reported. In summary, there is no confirmed evidence from human studies of increased cancer risk with OCs. Close surveillance is, however, essential. In undiagnosed persistent or recurrent abnormal vaginal bleeding, consider nonfunctional causes and take appropriate diagnostic measures to rule out malignancy. Carefully monitor users with a strong family history of breast cancer or with breast nodules, fibrocystic disease, recurrent cystic mastitis, abnormal mammograms, or cervical dysplasia. **4.** Hepatic adenomas, hepatomas, hamartomas, regenerating nodules, focal nodular hyperplasia, hemangiomas, hepatocellular carcinoma, etc. have been associated with OCs. In 1 study OC formulations with high "hormonal potency" were associated with higher risk. Though benign these hepatic lesions may rupture and cause fatal hemoperitoneum in short- or long-term users. Two studies related risk to duration of use, being much greater after ≥4 years. Consider such lesions in users with abdominal pain, tenderness, mass or shock. About 25% present with abdominal masses; up to half with acute hemoperitoneum. Routine radiologic and lab studies may not be helpful; liver scans may show a focal defect. Hepatic arteriography or CAT may be useful in diagnosis. Hepatocellular carcinoma was noted in a few users. OCs are contraindicated in case of past or present, benign or malignant liver tumors. **5.** Use in or immediately preceding pregnancy, birth defects, malignancy in offspring—Estrogens or progestogens during early pregnancy may seriously damage offspring. Females exposed in utero to DES and other nonsteroidal estrogens may have increased risk of vaginal or cervical cancer. Though OCs may not enhance this risk, monitor such patients carefully. From 30–90% of DES-exposed women develop benign vaginal or cervical adenosis, which could be premalignant. Males so exposed may develop urogenital defects. Other estrogens may mimic DES. Reports relate fetal exposure to female sex hormones and congenital anomalies, e.g., multiple anomalies described by VACTERL for vertebral, anal, cardiac, tracheoesophageal, renal and limb defects. There appears preferential expression by males. There was a 4.7-fold increased risk of limb-reduction defects in infants exposed in utero to sex hormones (OCs, hormonal withdrawal pregnancy tests or treatment for threatened abortion). Some exposures were very short, being only a few days. Cardiovascular defects in children exposed to female hormones, including OCs, during early pregnancy occurred at 18.2/1000 births, compared to 7.8 for those unexposed ($P<.05$). Female sex hormones were used for threatened or habitual abortion, but there is considerable evidence estrogens are ineffective and no evidence progestogens are effective. Triploidy and possibly other polyploidy may be increased in abortuses from women becoming pregnant soon post-OC. These almost always abort spontaneously. It is unknown if spontaneous abortion is increased soon after stopping OCs. Safety of OCs in pregnancy has not been demonstrated. Rule out pregnancy in using OCs and always consider it if withdrawal bleeding does not occur. If 2 consecutive periods are missed rule out pregnancy before continuing. If user deviates from regimen, consider pregnancy at first missed period and withhold OCs. If pregnancy is confirmed, apprise patient of potential fetal risks and discuss continuation of pregnancy. Users discontinuing for pregnancy should use alternative contraception for 3 months before attempting to conceive, though this is not based on precise information. Do not use progestogen-only or progestogen-estrogen drugs as pregnancy tests. **6.** Gallbladder disease risk, surgically confirmed, appeared after 2 years' use and doubled after 4–5 years in 1 study; it appeared in 6–12 months' use in another. **7.** Carbohydrate & lipid metabolism—Decreased glucose tolerance occurs in a significant number of users; carefully observe diabetic and prediabetic patients. Triglycerides and total phospholipids may increase. **8.** Elevated blood pressure (BP) occurs in some users in a few months, and degree may relate to progestogen dose. Hypertension prevalence in users is no higher than in nonusers in the first year, but increases with longer exposure; in the 5th year it is 2½–3 times the first year. Age is strongly correlated with hypertension in users. Those with history of elevated BP (hypertension), pre-existing renal disease, history of toxemia or elevated BP in pregnancy, familial tendency to hypertension or its consequences, or history of excessive weight gain or fluid retention during menstrual cycles may be more likely to develop elevated BP on OCs and thus should be monitored closely. Even though elevated BP may be in the "normal" range, do not ignore clinical implications. Follow closely, particularly those with other risk factors for cardiovascular disease or stroke. High BP may or may not persist after stopping OCs. **9.** Headache—Onset or exacerbation of migraine or development of headache of a new pattern that is recurrent, persistent or severe requires stopping OCs and evaluating cause. **10.** Bleeding irregularities—Breakthrough bleeding (BTB), spotting and amenorrhea are frequent reasons for discontinuing. In BTB, as in all cases of irregular bleeding, consider nonfunctional causes. In undiagnosed persistent or recurrent bleeding, rule out pregnancy or malignancy. If pathology is excluded, time or change to another product may suffice. Change to a higher estrogen OC only when necessary as this may increase thromboembolic risk. Those with a history of oligomenorrhea or secondary amenorrhea or without established regular cycles may be anovulatory or amenorrheic after discontinuing. Those with such problems should be so informed and other methods encouraged. Post-use anovulation, possibly prolonged, may occur in women without previous irregularities. Higher incidence of galactorrhea and of pituitary tumors (e.g., adenomas) has been associated with postpill amenorrhea. One study reported 16-fold increased prevalence of pituitary prolactin-secreting tumors in patients with postpill amenorrhea when galactorrhea was present. **11.** Ectopics—In failures with combination OCs, the ratio of ectopic to intrauterine pregnancies is no higher than in nonusers. There may be an increased risk of ectopics after discontinuing. **12.** Breast feeding—OCs may decrease quantity and quality of milk. A small fraction of OC steroids appears in milk. Effects if any on the child are unknown. If feasible defer OCs until after weaning. **13.** Infertility may occur in women discontinuing OCs, which appears independent of duration of use. While impairment diminishes with time, there is still an appreciable difference in nulliparous but not parous women after 30 months; difference is negligible after 42 months.

Precautions—Conduct complete history and physical prior to OC use and annually thereafter. Include breasts, abdomen and pelvis, with BP, pap and lab tests. Pre-existing uterine leiomyomata may enlarge. Mental depression may occur, with positive history, observe carefully and discontinue if serious recurrence. Fluid retention may occur; prescribe cautiously and monitor carefully in convulsive disorders, migraine, asthma, or cardiac, hepatic or renal dysfunction. History of jaundice in pregnancy increases risk of recurrence on OCs; observe carefully and discontinue if jaundice occurs. Steroids may be poorly metabolized in liver dysfunction and should be given cautiously. Tryptophan metabolism may be disturbed and result in pyridoxine deficiency; megaloblastic anemia has been reported. Serum folate may be depressed and may be exacerbated in post-OC pregnancy. Advise pathologist of OC use when submitting specimens. Endocrine and liver function tests may be altered; repeat abnormal tests after stopping for 2 months. These have been observed: increased BSP retention and other abnormalities in liver function tests; increased prothrombin and coagulation factors VII, VIII, IX, X; decreased antithrombin III, increased platelet aggregability; increased thyroid-binding globulin leading to increased circulating total thyroid hormone (PBI, T^4); decreased T^3 uptake, unaltered free T^4; decreased pregnanediol excretion; reduced metyrapone response; increased blood transcortin, corticosteroid, triglyceride, phospholipid; reduced serum folate; impaired glucose tolerance; altered plasma trace minerals. Influence of prolonged OC use on pituitary, ovarian, adrenal, hepatic, or uterine function, or on immune response is not established. OCs may mask onset of climacteric. Information for patients—see patient labeling. Drug interactions—OC effectiveness may be decreased and more BTB occur with rifampicin, isoniazid, ampicillin, neomycin, penicillin V, chloramphenicol, sulfonamides, nitrofurantoin, barbiturates, phenytoin, primidone, phenylbutazone, analgesics, tranquilizers, antimigraines. OCs may alter effectiveness of drugs such as oral anticoagulants, anticonvulsants, tricyclic antidepressants, antihypertensives, vitamins, hypoglycemics.

Adverse Reactions—Increased risk of the following serious adverse reactions has been associated with OCs: thrombophlebitis and thrombosis; pulmonary embolism; myocardial infarction and coronary thrombosis; cerebral thrombosis; cerebral hemorrhage; hypertension; gallbladder disease; benign adenomas and other hepatic lesions, with or without intra-abdominal bleeding; congenital abnormalities. There is evidence of association between the following conditions and OCs, though confirmatory studies have not been done: mesenteric thrombosis; Budd-Chiari syndrome, neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis. The following have been reported with OCs and are believed drug related: nausea, vomiting, gastrointestinal symptoms, breakthrough bleeding, spotting, change in menstrual flow, dysmenorrhea, amenorrhea during and after use, infertility post-OC, edema, chloasma or melasma, which may persist post-OC, breast changes (tenderness, enlargement, secretion), weight changes, change in cervical erosion and secretion, endocervical hyperplasia, lactation decrease, cholestatic jaundice, migraine, enlarged uterine leiomyomata, allergic rash, mental depression, reduced carbohydrate tolerance, vaginal candidiasis, change in corneal curvature (steepening), intolerance to contact lenses. The following have been reported and association has not been confirmed or refuted: premenstrual-like syndrome, cataracts, libido changes, chorea, appetite changes, cystitis-like syndrome, headache, paresthesia, nervousness, dizziness, auditory disturbances, rhinitis, fatigue, backache, hirsutism, scalp hair loss, erythema multiforme or nodosum, hemorrhagic eruption, itching, vaginitis, porphyria, impaired renal function, anemia, pancreatitis, hepatitis, colitis, gingivitis, lupus erythematosus, rheumatoid arthritis, pituitary tumors (e.g., adenoma) with amenorrhea and/or galactorrhea after use, endometrial, cervical and breast carcinoma.

Acute overdosage—Serious ill effects have not been reported after large acute doses of OCs in young children, but nausea and withdrawal bleeding might occur.

Important note—Full prescribing information should be consulted prior to use and is available on request.

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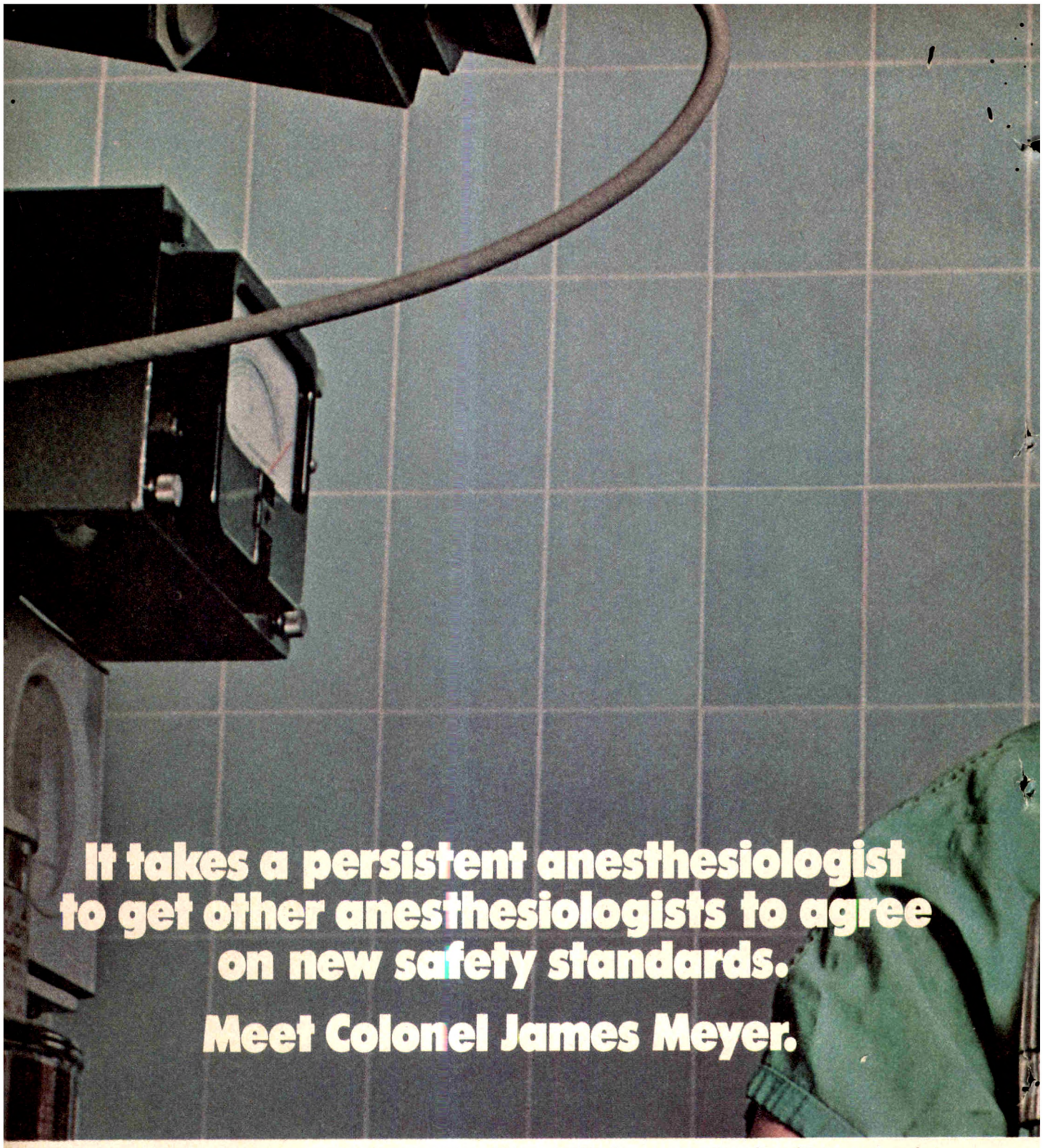
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It takes a persistent anesthesiologist to get other anesthesiologists to agree on new safety standards.

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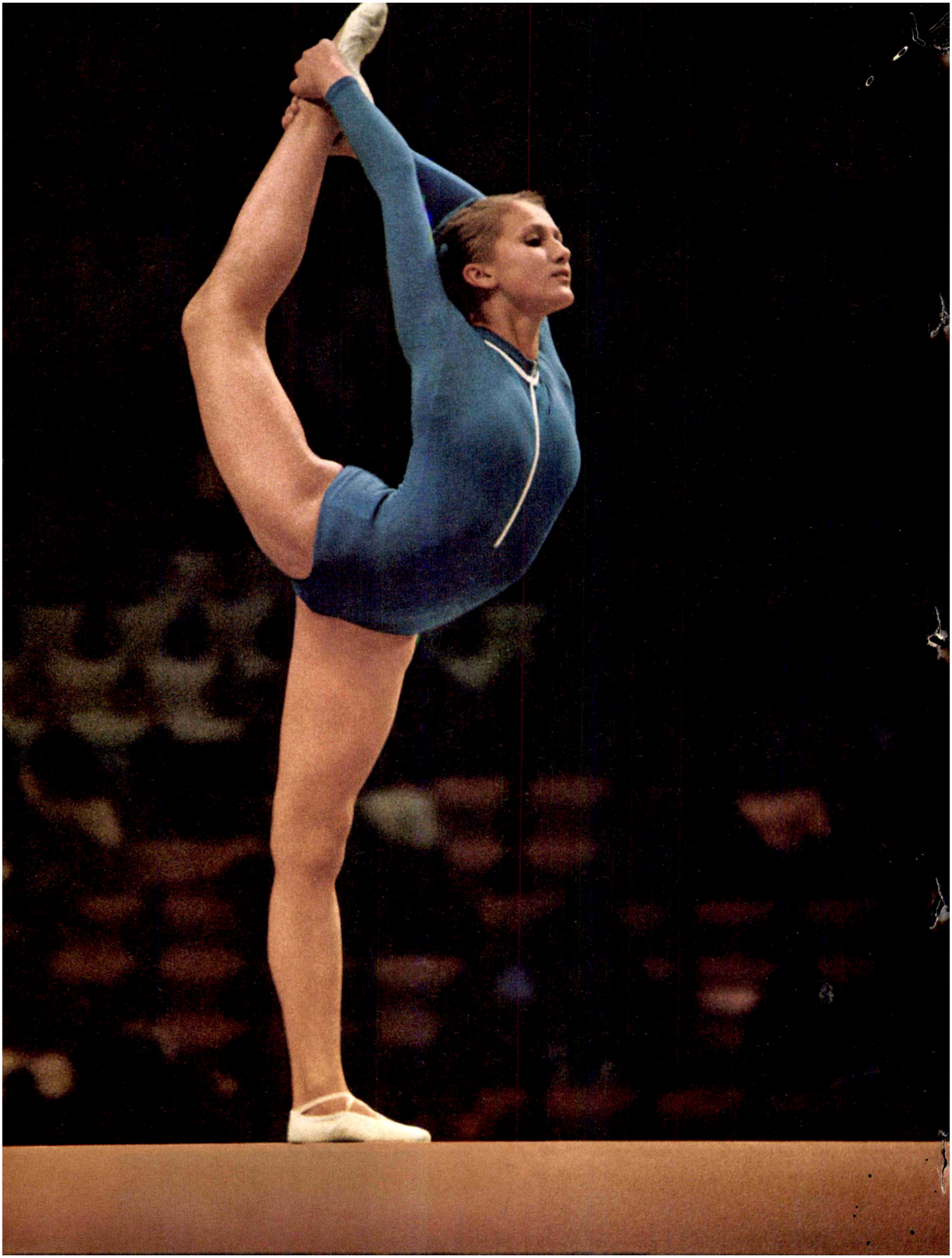
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†Serious as well as minor side effects have been reported with the use of oral contraceptives. These include thromboembolic disease. The physician should remain alert to the earliest manifestations of any symptoms of serious disease and discontinue oral contraceptive therapy when appropriate. The physician should be fully aware of the complete Prescribing Information for this product.

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- **INDICATION: CONTRACEPTION.** The pregnancy rate in women using conventional combination oral contraceptives (containing 35 mcg or more of ethinyl estradiol or 50 mcg or more of mestranol) is generally reported as less than one pregnancy per 100 woman-years of use. Slightly higher rates (somewhat more than one pregnancy per 100 woman-years of use) are reported for some combination products containing 35 mcg or less of ethinyl estradiol, and rates on the order of three pregnancies per 100 woman-years are reported for the progestogen-only oral contraceptives. Table 1 gives ranges of pregnancy rates reported in the literature for other means of contraception. The efficacy of these means of contraception (except the IUD) depends upon the degree of adherence to the method.

Table 1: Pregnancies Per 100 Women-Years. IUD, less than 1-6; Diaphragm with spermicidal product (creams or jellies), 2-20; Condom, 3-36; Aerosol foams, 2-29; Jellies and creams, 4-36; Periodic abstinence (rhythm) all types, less than 1-47; 1. Calendar method, 14-47; 2. Temperature method, 1-20; 3. Temperature method—intercourse only in postovulatory phase, less than 1-7; 4. Mucus method, 1-25; No contraception, 60-80. **DOSE-RELATED RISK OF THROMBOEMBOLISM FROM ORAL CONTRACEPTIVES:** Two studies have shown a positive association between the dose of estrogens in oral contraceptives and the risk of thromboembolism. For this reason, it is prudent and in keeping with good principles of therapeutics to minimize exposure to estrogen. The oral contraceptive product prescribed for any given patient should be that product which contains the least amount of estrogen that is compatible with an acceptable pregnancy rate and patient acceptance. It is recommended that new acceptors of oral contraceptives be started on preparations containing .05 mg or less of estrogen. **CONTRAINDICATIONS:** Oral contraceptives should not be used in women with any of the following conditions: 1. Thrombophlebitis or thromboembolic disorders. 2. A past history of deep vein thrombophlebitis or thromboembolic disorders. 3. Cerebral vascular or coronary artery disease. 4. Known or suspected carcinoma of the breast. 5. Known or suspected estrogen-dependent neoplasia. 6. Undiagnosed, abnormal genital bleeding. 7. Known or suspected pregnancy (see WARNINGS, No. 5).

WARNINGS

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

The use of oral contraceptives is associated with increased risk of several serious conditions including thromboembolism, stroke, myocardial infarction, hepatic adenoma, gallbladder disease, hypertension. Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks.

1. THROMBOEMBOLIC DISORDERS AND OTHER VASCULAR PROBLEMS. An increased risk of thromboembolic and thrombotic disease associated with the use of oral contraceptives is well established. Four principal studies in Great Britain and three in the United States have demonstrated an increased risk of fatal and nonfatal venous thromboembolism and stroke, both hemorrhagic and thrombotic. These studies estimate that users of oral contraceptives are 4 to 11 times more likely than nonusers to develop these diseases without evident cause. Overall excess mortality due to pulmonary embolism or stroke is on the order of 1.0 to 3.5 deaths annually per 100,000 users and increases with age. **CEREBROVASCULAR DISORDERS:** In a collaborative American study of cerebrovascular disorders in women with and without predisposing causes, it was estimated that the risk of hemorrhagic stroke was 2.0 times greater in users than in nonusers and the risk of thrombotic stroke was 4.0 to 9.5 times greater in users than in nonusers.

MYOCARDIAL INFARCTION: An increased risk of myocardial infarction associated with the use of oral contraceptives has been reported confirming a previously suspected association. These studies, conducted in the United Kingdom, found, as expected, that the greater the number of underlying risk factors for coronary artery disease (cigarette smoking, hypertension, hypercholesterolemia, obesity, diabetes, history of preeclamptic toxemia), the higher the risk of developing myocardial infarction, regardless of whether the patient was an oral contraceptive user or not. Oral contraceptives, however, were found to be a clear additional risk factor. The annual excess case rate (increased risk) of myocardial infarction (fatal and nonfatal) in oral contraceptive users was estimated to be approximately 7 cases per 100,000 women users in the 30-39 age group and 67 cases per 100,000 women users in the 40-44 age group. In terms of relative risk, it has been estimated that oral contraceptive users who do not smoke (smoking is considered a major predisposing condition to myocardial infarction) are about twice as likely to have a fatal myocardial infarction as nonusers who do not smoke. Oral contraceptive users who are also smokers have about a 5-fold increased risk of fatal infarction compared to users who do not smoke, but about a 10-to 12-fold increased risk compared to nonusers who do not smoke. Furthermore, the amount of smoking is also an important factor. In determining the importance of these relative risks, however, the baseline rates for various age groups must be given serious consideration. The importance of other predisposing conditions mentioned above in determining relative and absolute risks has not as yet been quantified; it is quite likely that the same synergistic action exists, but perhaps to a lesser extent. **Risk of Dose:** In an analysis of data derived from several national adverse reaction reporting systems, British investigators concluded that the risk of thromboembolism including coronary thrombosis is directly related to the dose of estrogen used in oral contraceptives. Preparations containing 100 mcg or more of estrogen were associated with a higher risk of thromboembolism than those containing 50-80 mcg of estrogen. Their analysis did suggest, however, that the quantity of estrogen may not be the sole factor involved. This finding has been confirmed in the United States. Careful epidemiological studies to determine the degree of thromboembolic risk associated with progestogen-only oral contraceptives have not been performed. Cases of thromboembolic disease have been reported in women using these products, and they should not be presumed to be free of excess risk. The risk of thromboembolic and thrombotic disorders, in both users and nonusers of oral contraceptives, increases with age. Oral contraceptive use, however, an independent risk factor for these events. **ESTIMATE OF EXCESS MORTALITY FROM CIRCULATORY DISEASES:** A large prospective study carried out in the United Kingdom estimated the mortality rate per 100,000 women per year from diseases of the circulatory system for users and nonusers of oral contraceptives according to age, smoking habits, and duration of use. The overall excess death rate annually from circulatory diseases for oral contraceptive users was estimated to be 20 per 100,000 (ages 15-34—5/100,000; ages 35-44—33/100,000; ages 45-49—140/100,000), the risk being concentrated in older women, in those with a long duration of use, and in cigarette smokers. It was not possible, however, to examine the interrelationships of age, smoking, and duration of use, nor to compare the effects of continuous versus intermittent use. Although the study showed a 10-fold increase in death due to circulatory diseases in users for five or more years, all of these deaths occurred in women 35 or older. Until larger numbers of women under 35 with continuous use for five or more years are available, it is not possible to assess the magnitude of the relative risk for this younger age group. This study reports that the increased risk of circulatory diseases may persist after the pill is discontinued. Another study published at the same time confirms a previously reported increase of mortality in pill users from cardiovascular disease. The available data from a variety of sources have been analyzed to estimate the risk of death associated with various methods of contraception. The estimates of risk of death for each method include the combined risk of the contraceptive method (e.g., thromboembolic and thrombotic disease in the case of oral contraceptives) plus the risk attributable to pregnancy or abortion in the event of method failure. This latter risk varies with the effectiveness of the contraceptive method. The findings of this analysis are shown in Figure 1 below. The study concluded that the mortality associated with all methods of birth control is low and below that associated with childbirth, with the exception of oral contraceptives in women over 40 who smoke. (The rates given for pill only/smokers for each age group are for smokers as a class. For "heavy" smokers [more than 15 cigarettes a day], the rates given would be about double; for "light" smokers [less than 15 cigarettes a day], about 50 percent.) The mortality associated with oral contraceptive use in nonsmokers over 40 is higher than with any other method of contraception in that age group. The lowest mortality is associated with the condom or diaphragm backed up by early abortion. The risk of thromboembolic and thrombotic disease associated with oral contraceptives increases with age after approximately age 30 and, for myocardial infarction, is further increased by hypertension, hypercholesterolemia, obesity, diabetes, or history of preeclamptic toxemia and especially by cigarette smoking. The risk of myocardial infarction in oral contraceptive users is substantially increased in women age 40 and over, especially those with other risk factors. Based on the data currently available, the following chart gives a gross estimate of the risk of death from circulatory disorders associated with the use of oral contraceptives:

SMOKING HABITS AND OTHER PREDISPOSING CONDITIONS—RISK ASSOCIATED WITH USE OF ORAL CONTRACEPTIVES

Age	Below 30	30-39	40+	
Heavy smokers	C	B	A	A—Use associated with very high risk.
Light smokers	D	C	B	B—Use associated with high risk.
Nonsmokers (no predisposing conditions)	D	C,D	C	C—Use associated with moderate risk.
Nonsmokers (other predisposing conditions)	C	C,B	B,A	D—Use associated with low risk.

The physician and the patient should be alert to the earliest manifestations of thromboembolic and thrombotic disorders (e.g., thrombophlebitis, pulmonary embolism, cerebrovascular insufficiency, coronary occlusion, retinal thrombosis, and mesenteric thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately. A four- to six-fold increased risk of postsurgery thromboembolic complications has been reported in oral contraceptive users. If feasible, oral contraceptives should be discontinued at least four weeks before surgery of a type associated with an increased risk of thromboembolism or prolonged immobilization. 2. OCULAR LESIONS. There have been reports of neuro-ocular lesions such as optic neuritis or retinal thrombosis associated with the use of oral contraceptives. Discontinue oral contraceptive medication if there is unexplained, sudden or gradual, partial or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal vascular lesions and institute appropriate diagnostic and therapeutic measures. 3. CARCINOMA. Long-term continuous administration of either natural or synthetic estrogen in certain animal species increases the frequency of carcinoma of the breast, cervix, vagina, and liver. Certain synthetic progestogens, none currently contained in oral contraceptives, have been noted to increase the incidence of mammary nodules, benign and malignant, in dogs. In humans, three case control studies have reported an increased risk of endometrial carcinoma associated with the prolonged use of exogenous estrogen in postmenopausal women. One publication reported on the first 21 cases submitted by physicians to a registry of cases of adenocarcinoma of the endometrium in women under 40 on oral contraceptives. Of the cases found in women without predisposing risk factors for adenocarcinoma of the endometrium (e.g., irregular bleeding at the time oral contraceptives were first given, polycystic ovaries), nearly all occurred in women who had used a sequential oral contraceptive. These products are no longer marketed. No evidence has been reported suggesting an increased risk of endometrial cancer in users of conventional combination or progestogen-only oral contraceptives. Several studies have found no increases in breast cancer in women taking oral contraceptives or estrogens. One study, however, while also noting no overall increased risk of breast cancer in women treated with oral contraceptives, found an excess risk in the subgroups of oral contraceptive users with documented benign breast disease. A reduced occurrence of benign breast tumors in users of oral contraceptives has been well-documented. In summary, there is at present no confirmed evidence from human studies of an increased risk of cancer associated with oral contraceptives. Close clinical surveillance of all women taking oral contraceptives is, nevertheless, essential. In all cases of undiagnosed persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be taken to rule out malignancy. Women with a strong family history of

Figure 1. Estimated annual number of deaths associated with control of fertility and no control per 100,000 nonsterile women, by regimen of control and age of woman.

	15-19	20-24	25-29	30-34	35-39	40-44
No method	5.5	5.2	7.1	14.0	19.3	21.9
Abortion only	2.3	2.5	2.5	5.2	9.8	6.6
Pill only-nonsmokers	1.3	1.4	1.4	2.2	4.5	3.1
Pill only-smokers	1.5	1.6	1.6	10.8	13.4	58.9
IUDs only	1.1	1.2	1.2	1.4	1.6	1.4
Traditional contraception only	1.1	1.4	1.9	3.7	4.7	4.0
Traditional contraception and abortion	0.3	0.4	0.4	0.8	1.4	0.8

4. HEPATIC TUMORS. Benign hepatic adenomas have been found to be associated with the use of oral contraceptives. One study showed that oral contraceptive formulations with high hormonal potency were associated with a higher risk than lower potency formulations. Although benign, hepatic adenomas may rupture and may cause death through intra-abdominal hemorrhage. This has been reported in short-term as well as long-term users of oral contraceptives. Two studies relate risk with duration of use of the contraceptive, the risk being much greater after four or more years of oral contraceptive use. While hepatic adenoma is a rare lesion, it should be considered in women presenting abdominal pain and tenderness, abdominal mass or shock. A few cases of hepatocellular carcinoma have been reported in women taking oral contraceptives. The relationship of these drugs to this type of malignancy is not known at this time. 5. USE IN OR IMMEDIATELY PRECEDING PREGNANCY, BIRTH DEFECTS IN OFFSPRING, AND MALIGNANCY IN FEMALE OFFSPRING. The use of female sex hormones—both estrogenic and progestational agents—during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a nonsteroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare. This risk has been estimated to be on the order of 1 to 4 in 1000 exposures. Although there is no evidence at the present time that oral contraceptives further enhance the risk of developing this type of malignancy, such patients should be monitored with particular care if they elect to use oral contraceptives instead of other methods of contraception. Furthermore, a high percentage of such exposed women (from 30 to 90%) have been found to have epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether this condition is a precursor of vaginal malignancy. Male children so exposed may develop abnormalities of the urogenital tract. Although similar data are not available with the use of other estrogens, it cannot be presumed that they would not induce similar changes. An increased risk of congenital anomalies, including heart defects and limb defects, has been reported with the use of sex hormones, including oral contraceptives, in pregnancy. One case control study has estimated a 4.7-fold increase in risk of limb-reduction defects in infants exposed in utero to sex hormones (oral contraceptives, hormonal withdrawal tests for pregnancy or attempted treatment for threatened abortion). Some of these exposures were very short and involved only a few days of treatment. The data suggest that the risk of limb-reduction defects in exposed fetuses is somewhat less than one in 1,000 live births. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well-controlled studies that progestogens are effective for these uses. There is some evidence that triploidy and possibly other types of polyploidy are increased among abortuses from women who become pregnant soon after ceasing oral contraceptives. Embryos with these anomalies are virtually always aborted spontaneously. Whether there is an overall increase in spontaneous abortion of pregnancies conceived soon after stopping oral contraceptives is unknown. It is recommended that for any patient who has missed two consecutive periods, pregnancy should be ruled out before continuing the contraceptive regimen. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at the time of the first missed period (or after 45 days from the last menstrual period if the progestogen-only oral contraceptives are used), and further use of oral contraceptives should be withheld until pregnancy has been ruled out. If pregnancy is confirmed, the patient should be apprised of the potential risks to the fetus and the advisability of continuation of the pregnancy should be discussed in the light of these risks. It is also recommended that women who discontinue oral contraceptives with the intent of becoming pregnant use an alternate form of contraception for a period of time before attempting to conceive. Many clinicians recommend three months although no precise information is available on which to base this recommendation. The administration of progestogen-only or progestogen-estrogen combinations to induce withdrawal bleeding should not be used as a test of pregnancy. 6. GALLBLADDER DISEASE. Studies report an increased risk of surgically confirmed gallbladder disease in users of oral contraceptives and estrogens. In one study, an increased risk appeared after two years of use and doubled after four or five years of use. In one of the other studies, an increased risk was apparent between six and twelve months of use. 7. CARBOHYDRATE AND LIPID METABOLIC EFFECTS. A decrease in glucose tolerance has been observed in a significant percentage of patients on oral contraceptives. For this reason, prediabetic and diabetic patients should be carefully observed while receiving oral contraceptives. An increase in triglycerides and total phospholipids has been observed in patients receiving oral contraceptives. The clinical significance of this finding remains to be defined. 8. ELEVATED BLOOD PRESSURE. An increase in blood pressure has been reported in patients receiving oral contraceptives. In some women hypertension may occur within a few months of beginning oral contraceptive use. In the first year of use, the prevalence of women with hypertension is low in users and may be no higher than that of a comparable group of nonusers. The prevalence in users increases, however, with longer exposure, and in the fifth year of use is two and a half to three times the reported prevalence in the first year. Age is also strongly correlated with the development of hypertension in oral contraceptive users. Women who previously have had hypertension during pregnancy may be more likely to develop elevation of blood pressure when given oral contraceptives. Hypertension that develops as a result of taking oral contraceptives usually returns to normal after discontinuing the drug. 9. HEADACHE. The onset or exacerbation of migraine or development of headache of a new pattern which is recurrent, persistent, or severe, requires discontinuation of oral contraceptives and evaluation of the cause. 10. BLEEDING IRREGULARITIES. Breakthrough bleeding, spotting, and amenorrhea are frequent reasons for patients discontinuing oral contraceptives. In breakthrough bleeding, as in all cases of irregular bleeding from the vagina, nonfunctional causes should be borne in mind. In undiagnosed persistent or recurrent abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy. If pathology has been excluded, time or a change to another formulation may solve the problem. Changing to an oral contraceptive with a higher estrogen content, while potentially useful in minimizing menstrual irregularity, should be done only if necessary since this may increase the risk of thromboembolic disease. Women with a past history of oligomenorrhea or secondary amenorrhea or young women without regular cycles may have a tendency to remain anovulatory or to become amenorrheic after discontinuation of oral contraceptives. Women with these preexisting problems should be advised of this possibility and encouraged to use other contraceptive methods. Postuse anovulation, possibly prolonged, may also occur in women without previous irregularities. 11. ECTOPIC PREGNANCY. Ectopic as well as intrauterine pregnancy may occur in contraceptive failures. 12. BREAST FEEDING. Oral contraceptives given in the postpartum period may interfere with lactation. There may be a decrease in the quantity and quality of the breast milk. Furthermore, a small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs. The effects, if any, on the breast-fed child have not been determined. If feasible, the use of oral contraceptives should be deferred until the infant has been weaned. **PRECAUTIONS: General:** 1. A complete medical and family history should be taken prior to the initiation of oral contraceptives. The pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen and pelvic organs, including Papanicolaou smear and relevant laboratory tests. As a general rule, oral contraceptives should not be prescribed for longer than one year without another physical examination being performed. 2. Under the influence of estrogen-progestogen preparations, preexisting uterine leiomyomata may increase in size. 3. Patients with a history of psychic depression should be carefully observed and the drug discontinued if depression recurs to a serious degree. Patients becoming significantly depressed while taking oral contraceptives should stop the medication and use an alternate method of contraception in an attempt to determine whether the symptom is drug-related. 4. Oral contraceptives may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention, such as convulsive disorders, migraine syndrome, asthma, or cardiac or renal insufficiency. 5. Patients with a past history of jaundice during pregnancy have an increased risk of recurrence of jaundice while receiving oral contraceptive therapy. If jaundice develops in any patient receiving such drugs, the medication should be discontinued. 6. Steroid hormones may be poorly metabolized in patients with impaired liver function and should be administered with caution in such patients. 7. Oral contraceptive users may have disturbances in normal tryptophan metabolism which may result in a relative pyridoxine deficiency. The clinical significance of this is yet to be determined. 8. Serum folate levels may be depressed by oral contraceptive therapy. Since the pregnant woman is predisposed to the development of folate deficiency and the incidence of folate deficiency increases with increasing gestation, it is possible that if a woman becomes pregnant shortly after stopping oral contraceptives, she may have a greater chance of developing folate deficiency and complications attributed to this deficiency. 9. The pathologist should be advised of oral contraceptive therapy when relevant specimens are submitted. 10. Certain endocrine and liver function tests and blood components may be affected by estrogen-containing oral contraceptives: a. Increased sulfobromophthalein retention. b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability. c. Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered. d. Decreased pregnanediol excretion. e. Reduced response to metyrapone test. **INFORMATION FOR THE PATIENT: (See Patient Package Insert). DRUG INTERACTIONS:** Reduced efficacy and increased incidence of breakthrough bleeding have been associated with concomitant use of rifampin. A similar association has been suggested with barbiturates, phenylbutazone, phenytoin sodium, and ampicillin. **CARCINOGENESIS, PREGNANCY, NURSING MOTHERS: See CONTRAINDICATIONS and WARNINGS. ADVERSE REACTIONS:** An increased risk of the following serious adverse reactions has been associated with the use of oral contraceptives (see WARNINGS): Thrombophlebitis. Pulmonary embolism. Coronary thrombosis. Cerebral thrombosis. Cerebral hemorrhage. Hypertension. Gallbladder disease. Liver tumors. Congenital anomalies. There is evidence of an association between the following conditions and the use of oral contraceptives, although additional confirmatory studies are needed: Mesenteric thrombosis. Neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis. The following adverse reactions have been reported in patients receiving oral contraceptives and are believed to be drug-related: Nausea, usually the most common adverse reaction. Vomiting, occurs in approximately 10% or less of patients during the first cycle. Other reactions, as a general rule, are seen much less frequently or only occasionally. Gastrointestinal symptoms (such as abdominal cramps and bloating). Breakthrough bleeding. Spotting. Change in menstrual flow. Dysmenorrhea. Amenorrhea during and after treatment. Temporary infertility after discontinuance of treatment. Edema. Chloasma or melasma which may persist. Breast changes: tenderness, enlargement, and secretion. Change in weight (increase or decrease). Change in cervical erosion and cervical secretion. Possible diminution in lactation when given immediately postpartum. Cholestatic jaundice. Migraine. Increase in size of uterine leiomyomata. Rash (allergic). Mental depression. Reduced tolerance to carbohydrates. Vaginal candidiasis. Change in corneal curvature (steepening). Intolerance to contact lenses. The following adverse reactions have been reported in users of oral contraceptives, and the association has been neither confirmed nor refuted: Premenstrual-like syndrome. Cataracts. Changes in libido. Chorea. Changes in appetite. Cystitis-like syndrome. Headache. Nervousness. Dizziness. Hirsutism. Loss of scalp hair. Erythema multiforme. Erythema nodosum. Hemorrhagic eruption. Vaginitis. Porphyria. Impaired renal function. (ORTHO-NOVUM 1/50□21 and ORTHO-NOVUM 1/50□28 contain tartrazine. Allergic reactions have been reported with the ingestion of this dye in some patients.) **ACUTE OVERDOSE:** Serious ill effects have not been reported following acute ingestion of large doses of oral contraceptives by young children. Overdosage may cause nausea, and withdrawal bleeding may occur in females.

ORTHO

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Submission of contributions. Manuscripts should in general be sent to a particular Editor according to the following plan: If it is from the southeastern quadrant of the United States or from Canada, or if it has been presented before one of the official sponsoring societies, to Dr. Brewer; if from the northeastern quadrant (including Ohio), or if it is a Clinical Opinion or a Letter to the Editors, to Dr. Zuspan; if from the north central states, any of the United States west of the Mississippi, Hawaii, Alaska, or abroad, to Dr. Quilligan.

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Tables should be typed on separate sheets of paper, not in the text, with one table to a page. They should be numbered in sequence and each must be referred to at an appropriate point in the text. Captions of the tables should be brief, yet indicate clearly the purpose or content of each table. Rows and columns in the table should precisely define the nature of the data in each. Abbreviations in tables should be used as little as possible and if abbreviations are used they should be explained in a footnote to the table.

An abstract of 50 to 150 words, to be published as an introduction, should accompany each manuscript and should be typed on a separate sheet of paper.

A footnote should be included which gives the name and complete mailing address of the person to whom reprint requests and correspondence should be sent.

A Guide to Writing for the American Journal of Obstetrics and Gynecology may be obtained from the Publisher on request.

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Letters to the Editors. A brief Letter to the Editors commenting upon some article which has appeared in the JOURNAL will be considered for publication. The writer of the original article will have an opportunity to reply to unfavorable comments. A brief case presentation of special interest in the form of a Letter to the Editors will also be considered for publication. All such letters should be sent to Dr. Zuspan.

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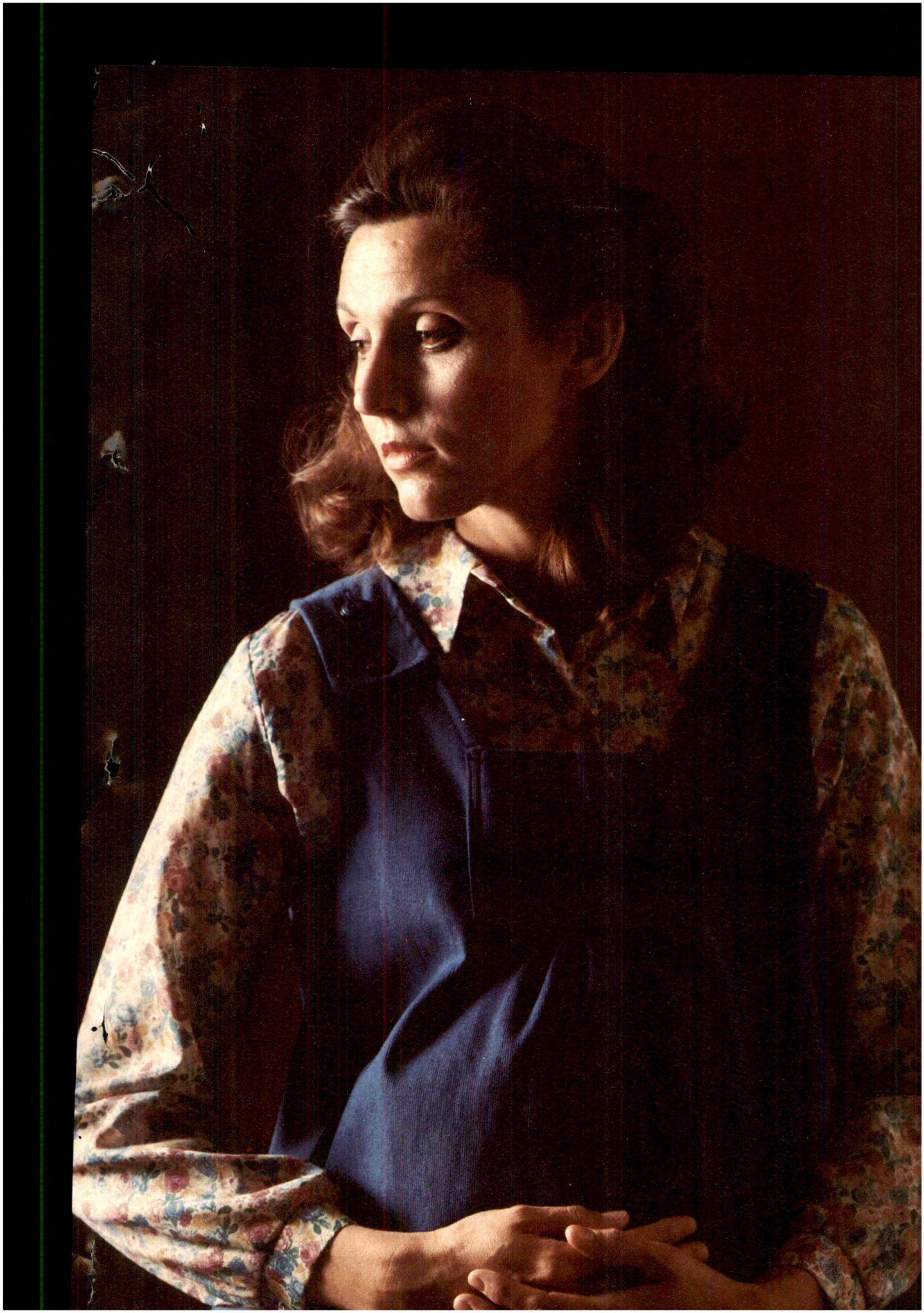
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"Nonspecific" vaginitis is often masked
"Nonspecific" vaginitis
...Often masked by previsit and routine douches, candidiasis and trichomoniasis.[1]
...Often chronic—in a recent clinical study of 5,000 consecutive cases of chronic vaginitis, the chief cause was undiagnosed H. vaginalis vaginitis, followed by candidiasis and trichomoniasis.[1]
1. Fleury, F.J.: Obstet. Gynecol. News 12:1,25, Aug. 15, 1977.
2. Gardner, H.L., and Kaufman, R.H.: Benign Diseases of the Vulva and Vagina, St. Louis, The C.V. Mosby Company, 1969, p. 191.

When you unmask "nonspecific" vaginitis you may find H. vaginalis

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Triple Sulfa Cream/Vaginal Tablets

effective against H.vaginalis— the cause of over 90% of "nonspecific" vaginitis[2]

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Based on a review by the National Academy of Sciences/National Research Council, SULTRIN was rated as "effective" against *H. vaginalis.*

Prompt symptomatic relief
Patients can experience relief of embarrassing itching and malodorous discharge. Within the same time, most patients can also achieve marked clinical improvement.

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SULTRIN is also effective in treating H.V. vaginitis concomitant with trichomoniasis and candidiasis.

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Contraindications: Sulfonamide sensitivity and kidney disease.

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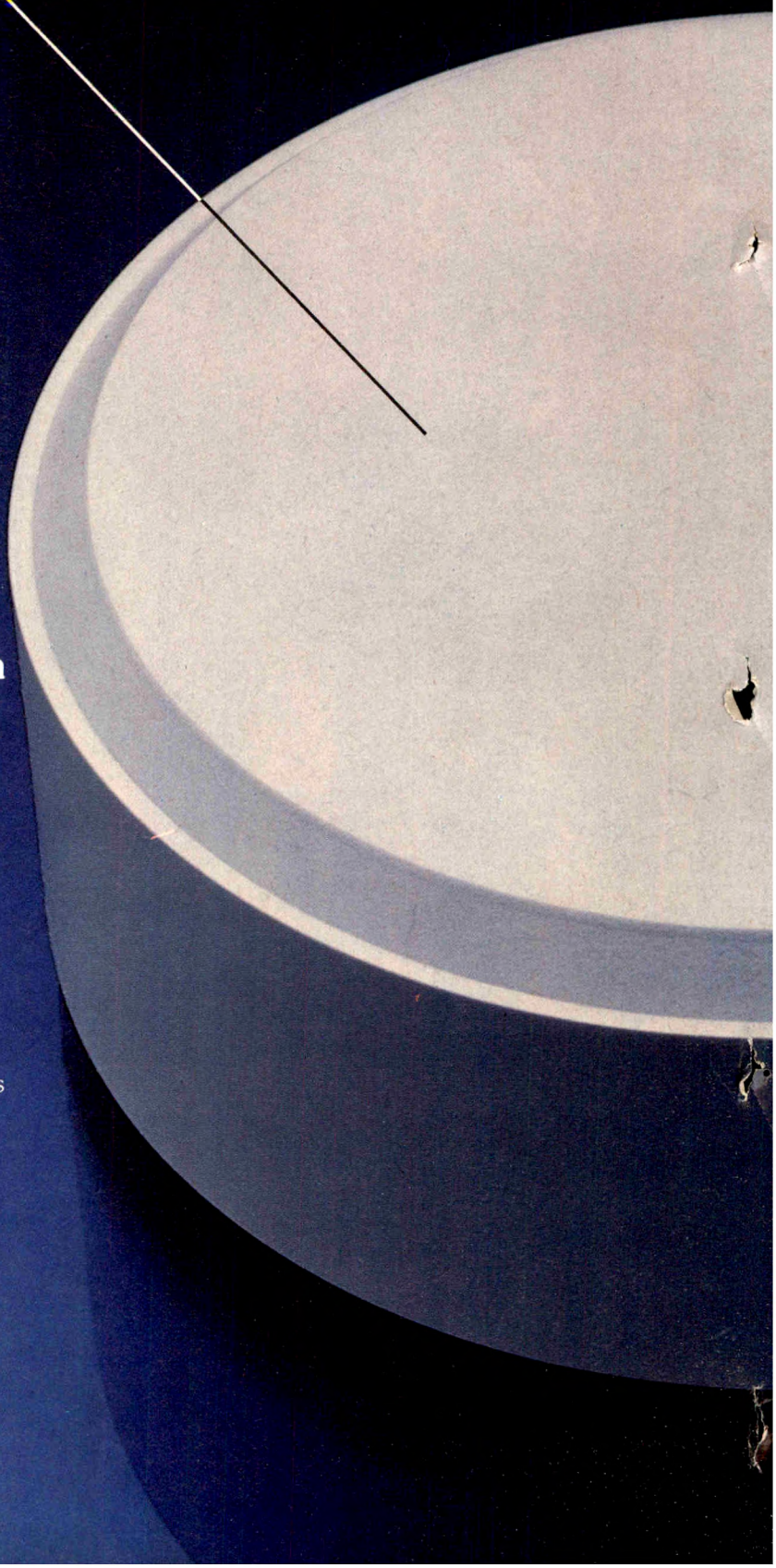
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The progestogen in oral contraceptives: But certainly



Norgestrel, the progestogen that distinguishes Ovral and Lo/Ovral.

Today, many physicians are concerned about choosing a suitable estrogen level for their oral contraceptive patients.

The effects of any combination oral contraceptive, however, are largely the result of the synergistic activity between estrogen and progestogen. So it seems wise to choose the progestogen carefully, too.

Norgestrel, the progestogen in Ovral and Lo/Ovral, has many properties worth examining.

Distinctive because it is non-estrogenic and does not add estrogen. Unlike other progestogens in current use, norgestrel has been shown in biological assays to be free from inherent estrogenicity and does not convert to estrogen *in vivo*. So the delicate estrogen-progestogen balance in Ovral and Lo/Ovral remains undisturbed.

It helps maintain a sound endometrium in combination with ethinyl estradiol. Even at very low doses, norgestrel demonstrates a pronounced ability to help support the integrity of the endometrium—a primary function of progestogen in oral contraceptives.

A highly effective estrogen antagonist. Norgestrel displays marked anti-estrogenic activity at the cervical level. It thickens the cervical mucus during the 3-week cycle of therapy and may therefore act as a secondary contraceptive mechanism.



Norgestrel and ethinyl estradiol: together they usually mean patient confidence, comfort and compliance. In separate clinical trials, overall effectiveness with Ovral over an 8 year period was 99.3 percent; with Lo/Ovral over a 4 year period, 99.7 percent.[1] Both Ovral and Lo/Ovral also offered excellent cycle control and a minimum of common side effects.* The drop-out rate due to breakthrough bleeding for Ovral was only 0.5 percent; for Lo/Ovral, only 1.4 percent.
50 mcg Ovral® and 30 mcg Lo/Ovral®: distinguished by norgestrel.

*Serious as well as minor adverse reactions have been reported following the use of all oral contraceptives. The physician should remain alert to their earliest manifestations and in the event of serious adverse reactions, should avoid any oral contraceptives. Contraindications, Warnings, Precautions, Adverse Reactions, etc. in the accompanying IN BRIEF should be carefully considered.

1. Based on life table method.

See important information on following page.

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OVRAL®
Each tablet contains 0.5 mg norgestrel with 0.05 mg ethinyl estradiol.

LO/OVRAL®
Each tablet contains 0.3 mg norgestrel with 0.03 mg ethinyl estradiol.

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IN BRIEF:

Indications and Usage—OVRAL® and LO/OVRAL® are indicated for the prevention of pregnancy in women who elect to use oral contraceptives (OC's) as a method of contraception.

Contraindications—OC's should not be used in women with any of the following conditions: 1. Thrombophlebitis or thromboembolic disorders. 2. A past history of deep-vein thrombophlebitis or thromboembolic disorders. 3. Cerebral-vascular or coronary-artery disease. 4. Known or suspected carcinoma of the breast. 5. Known or suspected estrogen-dependent neoplasia. 6. Undiagnosed abnormal genital bleeding. 7. Known or suspected pregnancy (see Warning No. 5).

Warnings

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

The use of oral contraceptives is associated with increased risk of several serious conditions, including thromboembolism, stroke, myocardial infarction, hepatic adenoma, gall bladder disease, hypertension. Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks.

1. *Thromboembolic Disorders and Other Vascular Problems:* An increased risk of thromboembolic and thrombotic disease associated with use of OC's is well-established. Three principal studies in Great Britain and 3 in the U.S. have demonstrated increased risk of fatal and nonfatal venous thromboembolism and stroke, both hemorrhagic and thrombotic. These studies estimate that users of OC's are 4 to 11 times more likely than nonusers to develop these diseases without evident cause.

CEREBROVASCULAR DISORDERS—In a collaborative American study of cerebrovascular disorders in women with and without predisposing causes, it was estimated that the risk of hemorrhagic stroke was 2.0 times greater in users than nonusers and the risk of thrombotic stroke was 4 to 9.5 times greater in users than in nonusers.

MYOCARDIAL INFARCTION (MI)—An increased risk of MI associated with use of OC's has been reported, confirming a previously suspected association. These studies, conducted in the UK, found, as expected, that the greater the number of underlying risk factors for coronary-artery disease (cigarette smoking, hypertension, hypercholesterolemia, obesity, diabetes, history of preeclamptic toxemia) the higher the risk of developing MI, regardless of whether the patient was an OC user or not. OC's, however, were found to be a clear additional risk factor. In terms of relative risk, it has been estimated that OC users who do not smoke (smoking is considered a major predisposing condition to MI) are about twice as likely to have a fatal MI as nonusers who do not smoke. OC users who are also smokers have about a 5-fold increased risk of fatal MI compared to users who do not smoke, but about a 10- to 12-fold increased risk compared to nonusers who do not smoke. Furthermore, amount of smoking is also an important factor. In determining importance of these relative risks, however, baseline rates for various age groups must be given serious consideration. Importance of other predisposing conditions mentioned above in determining relative and absolute risks has not as yet been quantified; quite likely the same synergistic action exists, but perhaps to a lesser extent.

RISK OF DOSE—In an analysis of data derived from several national adverse-reaction reporting systems, British investigators concluded that risk of thromboembolism, including coronary thrombosis, is directly related to dose of estrogen in OC's. Preparations containing 100 mcg or more of estrogen were associated with higher risk of thromboembolism than those containing 50-80 mcg. Their analysis did suggest, however, that quantity of estrogen may not be the sole factor involved. This finding has been confirmed in the U.S.

ESTIMATE OF EXCESS MORTALITY FROM CIRCULATORY DISEASES—A large prospective study carried out in the UK estimated the mortality rate per 100,000 women per year from diseases of the circulatory system for users and nonusers of OC's according to age, smoking habits, and duration of use. Overall excess death rate annually from circulatory diseases for OC users was estimated to be 20 per 100,000 (ages 15-34—5/100,000; ages 35-44—33/100,000; ages 45-49—140/100,000), risk being concentrated in older women, in those with long duration of use, and in cigarette smokers. It was not possible, however, to examine interrelationships of age, smoking, and duration of use, nor to compare effects of continuous vs. intermittent use. Although the study showed a 10-fold increase in death due to circulatory diseases in users for 5 or more years, all these deaths occurred in women 35 or older. Until larger numbers of women under 35 with continuous use for 5 or more years are available, it is not possible to assess magnitude of relative risk for this younger group.

Available data from a variety of sources have been analyzed to estimate risk of death associated with various methods of contraception. Estimates of risk of death for each method include combined risk of contraceptive method (e.g. thromboembolic and thrombotic disease in the case of OC's) plus risk attributable to pregnancy or abortion in event of method failure. This latter risk varies with effectiveness of method. The study concluded that mortality associated with all methods of birth control is low and below that associated with childbirth, with the exception of OC's in women over 40 who smoke. Lowest mortality is associated with condom or diaphragm backed up by early abortion. Risk of thromboembolic and thrombotic disease associated with OC's increases with age after about 30 and, for MI, is further increased by hypertension, hypercholesterolemia, obesity, diabetes, or history of preeclamptic toxemia, and especially cigarette smoking.

Physician and patient should be alert to earliest manifestations of thromboembolic and thrombotic disorders (e.g., thrombophlebitis, pulmonary embolism, cerebrovascular insufficiency, coronary occlusion, retinal thrombosis, and mesenteric thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately. A 4- to 6-fold increased risk of postsurgery thromboembolic complications has been reported in OC users. If feasible, OC's should be discontinued at least 4 weeks before surgery of a type associated with increased risk of thromboembolism or prolonged immobilization.

2. *Ocular Lesions*—There have been reports of neuro-ocular lesions such as optic neuritis or retinal thrombosis associated with use of OC's. Discontinue OC's if there is unexplained, sudden or gradual, partial or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal-vascular lesions, and institute appropriate diagnostic and therapeutic measures.

3. *Carcinoma*—Long-term continuous administration of either natural or synthetic estrogen in certain animal species increases frequency of carcinoma of the breast, cervix, vagina, and liver. Certain synthetic progestogens, none currently contained in OC's, have been noted to increase incidence of mammary nodules, benign and malignant, in dogs. In humans, 3 case-control studies have reported an increased risk of endometrial carcinoma associated with prolonged use of exogenous estrogen in postmenopausal women. One publication reported on the first 21 cases submitted by physicians to a registry of cases of adenocarcinoma of the endometrium in women under 40 on OC's. Of cases found in women without predisposing risk factors (e.g., irregular bleeding at the time OC's were first given, polycystic ovaries), nearly all occurred in women who had used a sequential OC. These are no longer marketed. No evidence has been reported suggesting increased risk of endometrial cancer in users of conventional combination or progestogen-only OC's. Several studies have found no increase in breast cancer in women taking OC's or estrogens. One study, however, while also noting no overall increased risk of breast cancer in women on OC's, found an excess risk in subgroups of OC users with documented benign breast disease. Reduced occurrence of benign breast tumors in users of OC's has been well-documented. In summary, there is at present no confirmed evidence from human studies of increased risk of cancer associated with OC's. Close clinical surveillance of all women on OC's is, nevertheless, essential. In all cases of undiagnosed persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be taken to rule out malignancy. Women with a strong family history of breast cancer or with breast nodules, fibrocystic disease, or abnormal mammograms should be monitored with particular care if they elect to use OC's.

4. *Hepatic Tumors*—Benign hepatic adenomas have been found to be associated with use of OC's. One study showed that OC's with high hormonal potency were associated with higher risk than lower potency OC's. Although benign, hepatic adenomas may rupture and may cause death through intra-abdominal hemorrhage. This has been reported in short-term as well as long-term users. Two studies relate risk with duration of use of OC's, the risk being much greater after 4 or more years' use. While hepatic adenoma is rare, it should be considered in women presenting abdominal pain and tenderness, abdominal mass or shock. A few cases of hepatocellular carcinoma have been reported in women on OC's. Relationship of these drugs to this type of malignancy is not known.

5. *Use in or Immediately Preceding Pregnancy, Birth Defects in Offspring, and Malignancy in Female Offspring*—Use of female sex hormones—both estrogenic and progestational agents—during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a nonsteroidal estrogen, have increased risk of developing in later life a form of vaginal or cervical cancer ordinarily extremely rare. This risk has been estimated to be of the order of 1 in 1,000 exposures or less. Although there is no evidence now that OC's further enhance risk of developing this type of malignancy, such patients should be monitored with particular care if they elect to use OC's. Furthermore, 30 to 90% of such exposed women have been found to have epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether this condition is a precursor of vaginal malignancy. Male children so exposed may develop abnormalities of the urogenital tract. Although similar data are not available with use of other estrogens, it cannot be presumed they would not induce similar changes. An increased risk of congenital anomalies, including heart defects and limb defects, has been reported with use of sex hormones, including OC's, in pregnancy. One case-control study estimated a 4.7-fold increase in risk of limb-reduction defects in infants exposed in utero to sex hormones (OC's, hormonal withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some exposures involved only a few days. Data suggest that risk of limb-reduction defects in exposed fetuses is somewhat less than 1 in 1,000 live births. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well-controlled studies that progestogens are effective. There is some evidence that triploidy and possibly other types of polyploidy are increased among abortuses from women who become pregnant soon after ceasing OC's. Embryos with these anomalies are virtually always aborted spontaneously. Whether there is an overall increase in spontaneous abortion of pregnancies conceived soon after stopping OC's is unknown. It is recommended that, for any patient who has missed 2 consecutive periods, pregnancy should be ruled out before continuing OC's. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at time of first missed period, and further use of OC's should be withheld until pregnancy has been ruled out. If pregnancy is confirmed, the patient should be apprised of the potential risks to the fetus, and advisability of continuation of the pregnancy should be discussed. It is also recommended that women who discontinue OC's with intent of becoming pregnant use an alternate form of contraception for a period of time before attempting to conceive. Many clinicians recommend 3 months, although no precise information is available on which to base this. The administration of progestogen-estrogen combinations to induce withdrawal bleeding should not be used as a test of pregnancy.

6. *Gallbladder Disease*—Studies report increased risk of surgically confirmed gallbladder disease in users of OC's and estrogens. In one study, increased risk appeared after 2 years' use and doubled after 4 or 5 years' use. In one of the other studies, increased risk was apparent between 6 and 12 months' use.

7. *Carbohydrate and Lipid Metabolic Effects*—Decrease in glucose tolerance has been observed in a significant percentage of patients on OC's. For this reason, prediabetic and diabetic patients should be carefully observed while on OC's. Increase in triglycerides and total phospholipids has been observed in patients on OC's; clinical significance of this finding remains to be defined.

8. *Elevated Blood Pressure*—Increase in blood pressure has been reported in patients on OC's. In some women, hypertension may occur within a few months of beginning OC's. In the 1st year of use, prevalence of women with hypertension is low in users and may be no higher than that of a comparable group of nonusers. Prevalence in users increases, however, with longer exposure, and in the 5th year of use is 2½ to 3 times the reported prevalence in the 1st year. Age is also strongly correlated with development of hypertension in OC users. Women who previously have had hypertension during pregnancy may be more likely to develop elevation of blood pressure on OC's. Hypertension that develops as a result of taking OC's usually returns to normal after discontinuing the drug.

9. *Headache*—Onset or exacerbation of migraine or development of headache of a new pattern which is recurrent, persistent, or severe, requires discontinuation of OC's and evaluation of the cause.

10. *Bleeding Irregularities*—Breakthrough bleeding, spotting, and amenorrhea are frequent reasons for patients discontinuing OC's. In breakthrough bleeding, as in all cases of irregular vaginal bleeding, nonfunctional causes should be borne in mind. In undiagnosed persistent or recurrent abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy. If pathology has been excluded, time or change to another OC may solve the problem. Changing to an OC with a higher estrogen content, while potentially useful in minimizing menstrual irregularity, should be done only if necessary, since this may increase risk of thromboembolic disease.

Women with past history of oligomenorrhea or secondary amenorrhea or young women without regular cycles may have a tendency to remain anovulatory or to become amenorrheic after discontinuing OC's. Women with these preexisting problems should be advised of this possibility and encouraged to use other methods. Post-use anovulation, possibly prolonged, may also occur in women without previous irregularities.

11. *Ectopic Pregnancy*—Ectopic as well as intrauterine pregnancy may occur in contraceptive failures.

12. *Breast-feeding*—OC's given in the postpartum period may interfere with lactation and decrease quantity and quality of breast milk. Furthermore, a small fraction of the hormones in OC's has been identified in the milk of mothers on OC's; effects, if any, on the breast-fed child have not been determined. If feasible, defer OC's until infant has been weaned.

Precautions—GENERAL—1. A complete medical and family history should be taken prior to initiation of OC's. Pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen and pelvic organs, including Pap smear and relevant laboratory tests. As a general rule OC's should not be prescribed for longer than 1 year without another physical examination.

2. Under influence of estrogen-progestogen preparations, pre-existing uterine leiomyomata may increase in size.

3. Patients with history of psychic depression should be carefully observed and the drug discontinued if depression recurs to a serious degree. Patients becoming significantly depressed while on OC's should stop OC's and use an alternate method to try to determine whether the symptom is drug-related.

4. OC's may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention, such as convulsive disorders, migraine syndrome, asthma, or cardiac or renal insufficiency.

5. Patients with a past history of jaundice during pregnancy have an increased risk of recurrence while on OC's. If jaundice develops, OC's should be discontinued.

6. Steroid hormones may be poorly metabolized in patients with impaired liver function and should be administered with caution.

7. OC users may have disturbances in normal tryptophan metabolism which may result in a relative pyridoxine deficiency. Clinical significance is undetermined.

8. Serum folate levels may be depressed by OC's. Since the pregnant woman is predisposed to development of folate deficiency and incidence of folate deficiency increases with increasing gestation, it is possible that if a woman becomes pregnant shortly after stopping OC's, she may have a greater chance of developing folate deficiency and complications attributed to this deficiency.

9. The pathologist should be advised of OC therapy when relevant specimens are submitted.

10. Certain endocrine- and liver-function tests and blood components may be affected by estrogen-containing OC's: a. Increased sulfobromophthalein retention. b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability. c. Increased thyroid-binding globulin (TBG) leading to increased circulating total-thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered. d. Decreased pregnanediol excretion. e. Reduced response to metyrapone test.

Information for the Patient—See Patient Package Labeling.

Drug Interactions—Reduced efficacy and increased incidence of breakthrough bleeding have been associated with concomitant use of rifampin. A similar association has been suggested with barbiturates, phenylbutazone, phenytoin sodium, and ampicillin.

Carcinogenesis—See Warnings on carcinogenic potential of OC's.

Pregnancy—Category X. See Contraindications, Warnings.

Nursing Mothers—See Warnings.

Adverse Reactions—An increased risk of these serious adverse reactions has been associated with use of OC's (see Warnings): thrombophlebitis, pulmonary embolism, coronary thrombosis, cerebral thrombosis, cerebral hemorrhage, hypertension, gallbladder disease, benign hepatomas, congenital anomalies. There is evidence of an association between the following conditions and use of OC's although additional confirmatory studies are needed: mesenteric thrombosis, neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis.

The following adverse reactions have been reported in patients on OC's and are believed to be drug-related. Nausea and/or vomiting, usually the most common adverse reactions, occur in approximately 10 percent or less of patients during the first cycle. Other reactions, as a general rule, are seen much less frequently or only occasionally. Gastrointestinal symptoms (such as abdominal cramps and bloating); breakthrough bleeding, spotting, change in menstrual flow; dysmenorrhea, amenorrhea during and after treatment, temporary infertility after discontinuance of treatment; edema; chloasma or melasma which may persist; breast changes: tenderness, enlargement, and secretion; change in weight (increase or decrease); change in cervical erosion and cervical secretion; possible diminution in lactation when given immediately postpartum; cholestatic jaundice; migraine; increase in size of uterine leiomyomata; rash (allergic); mental depression; reduced tolerance to carbohydrates; vaginal candidiasis; change in corneal curvature (steepening), intolerance to contact lenses.

The following adverse reactions have been reported in users of OC's, and the association has been neither confirmed nor refuted: premenstrual-like syndrome, cataracts, changes in libido, chorea, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption, vaginitis, porphyria.

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OBSTETRICS

Induction of labor following intrauterine death with intra-amniotic hyperosmolar urea and prostaglandin $F_{2\alpha}$: Evaluation of placental endocrine function and changes in coagulation parameters

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A practicable and reliable method for inducing labor in patients whose pregnancies are complicated by intrauterine death of the fetus is described. The method involves the intra-amniotic instillation of 30 mg of prostaglandin $F_{2\alpha}$ with 60 gm of urea. Twenty patients had pregnancies ranging between 22 and 41 weeks and the estimated duration of fetal death ranged between two and eight weeks. Delivery was achieved within 24 hours in all cases. Side effects and complications were minimal. Plasma human placental lactogen (hPL) and progesterone concentrations, as well as several blood coagulation parameters (i.e., plasma fibrinogen, blood platelet count, and serum fibrin degradation products (FDP) concentrations), were measured immediately prior to induction of labor. The latter (i.e., coagulation factors) were repeated at parturition. The presence of residual viable placenta prior to induction did not influence the induction-delivery interval. No statistically significant alterations in blood coagulation parameters that could be attributed to the specific method of induction employed were noted. (AM. J. OBSTET. GYNECOL. 134:493, 1979.)

IN MOST CASES, spontaneous labor and delivery follow within about two weeks of intrauterine death of the fetus.[1] In the event that this fails to occur, the obstetrician is often faced with the decision of whether or not to induce labor and thereby expedite delivery. The psychological distress to which a mother carrying a dead fetus is subjected, coupled with a time-related risk of the development of disseminated intravascular coagulation (DIC)[2, 3] makes urgent delivery not only desirous but, on occasion, imperative. The introduction of prostaglandins and their subsequent application (via the intravenous,[4, 5] intra-amniotic,[6] intrauterine–extra-amniotic,[3] and vaginal[6, 7] routes) for the management of pregnancies complicated by intrauterine death of the fetus heralded a new era in the treatment of this condition.

In 1976, the author reported on the management of 14 pregnancies (ranging between 17 and 35 weeks ges-

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Table I

Case No.	Age	Gravidity	Parity	Gestational age (wk.)	Estimated duration of fetal death (wk.)	Presumed cause of fetal death	Fundal height (cm.)	Induction/delivery interval (hr.)
1*	36	7	4	30	2	Diabetes mellitus	33	17
2*	24	3	3	26	4	—	22	12
3*	18	1	1	34	8	—	26	23
4	21	1	2	34	2	True knot in cord	31	4
5*	19	1	1	25	3	—	20	5
6*	15	1	0	18	3	—	16	19
7*	29	6	3	35	5	Placental insufficiency	28	9
8*	37	7	1	36	2	Positive serologic tests for syphilis	36	10
9	23	3	1	30	2	Anencephaly	30	6
10*	16	1	1	37	3	Pre-eclampsia	34	13
11*	28	1	1	31	6	—	22	16
12	33	2	2	34	2	Nephritis	32	23
13*	40	1	1	32	3	—	26	5
14*	32	4	4	41	2	Omphalocele	39	2
15*	40	8	6	40	2	—	39	21
16*	33	7	5	27	4	—	22	24
17*	19	1	1	31	2	—	24	5
18	25	2	1	36	2	Pre-eclampsia	36	20
19*	37	8	2	37	2	Diabetes	36	8
20*	24	5	2	22	2	—	18	2

PPH, Postpartum hemorrhage.
*No previous prenatal care.

tation) complicated by intrauterine death of the fetus that were managed by a single amniotic injection of 30 mg of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) and 60 gm of urea. Delivery resulted within 17 hours in all cases.[8] Complications were rare.

This larger study was undertaken in an effort to support the previous findings and to ascertain the extent to which this form of management would influence major blood coagulation parameters (i.e., plasma fibrinogen concentration, blood platelet count, and serum fibrin degradation products (FDP) concentrations) and the extent to which residual placental survival (evaluated by the measurement of plasma human placental lactogen [hPL] and progesterone concentrations) would influence induction-delivery interval in pregnancies complicated by intrauterine death of the fetus managed with intra-amniotic urea and prostaglandin. The study was conducted at the Groote Schuur Hospital, which is the teaching institution of the University of Cape Town School of Medicine, South Africa.

Patients, methods, and materials

Twenty patients with intrauterine death of the fetus were investigated. Death was diagnosed by clinical signs and symptoms and confirmed radiologically and/or by ultrasound examination. All fetuses were judged to have been dead for longer than 2 weeks. Details of each patient are presented in Table I.

Plasma concentrations of hPL and progesterone were measured immediately prior to commencing the intra-amniotic infusion of urea and $PGF_{2\alpha}$. Plasma fibrinogen concentrations (measured by the Haanen method[9, 10]), blood platelet count, (in parallel on the Coulter counter), and serum FDP (measured by hemagglutination inhibition) were measured in specimens of blood obtained both prior to induction and at the time of delivery (Table I). All patients were premedicated with diazepam. The abdomen was prepared as for a routine amniocentesis, using a strictly aseptic technique. A selected area of skin was infiltrated with 10 ml of a 1% Xylocaine solution. Thereafter, a No. 18 Tuohy needle was introduced transabdominally into the uterine cavity. About 100 ml of amniotic fluid was drained off, whereupon an epidural catheter was introduced into the amniotic sac through the Tuohy needle. Subsequent aspiration of amniotic fluid through the cannula reconfirmed its correct location. Sixty grams of urea, dissolved in 70 ml of normal saline solution, was introduced under pressure into the amni-

Complications	Plasma fibrinogen concentration (mg/dl)		Platelet count (per mm³)		Serum FDP (μg/ml)		Plasma HPL (μg/ml)	Plasma progesterone (ng/ml)
	Before induction	At delivery	Before induction	At delivery	Before induction	At delivery	Prior to induction	Prior to induction
PPH-700 ml. retained products	410	456	317,000	285,000	.5	7.7	3.4	42.5
—	406	403	259,000	260,000	2.5	12.9	1.7	9.5
Oxytocin infusion PPH->1,000 ml Atonic uterus	100	97	108,000	127,000	570.0	695.0	5.3	76.5
Retained products	720	685	198,000	131,000	4.9	7.8	4.3	76.5
Nausea/vomiting	197	253	292,000	356,000	—	—	1.5	15.9
—	270	203	225,000	224,000	3.3	13.0	1.3	17.9
—	275	270	198,000	171,000	7.5	11.3	<1.0	13.8
—	375	297	227,000	241,000	13.2	8.9	6.5	140.
Diarrhea/vomiting	203	268	124,000	124,000	6.6	10.4	3.4	52.
—	510	643	287,000	308,000	4.95	9.6	<1.0	9.7
—	540	511	198,000	196,000	2.47	14.9	<1.0	18.4
—	262	277	321,000	259,000	5.0	11.6	<1.0	13.9
—	432	463	254,000	199,000	1.23	8.9	<1.0	15.2
Transient pyrexia	760	598	195,000	198,000	12.5	7.5	4.73	127.0
Retained products	715	700	483,000	489,000	7.5	12.8	6.0	67.0
—	259	222	199,000	150,000	1.8	11.5	<1.0	11.5
Vomiting	379	363	285,000	253,000	1.6	—	1.45	19.7
Transient pyrexia	620	647	475,000	298,000	12.5	15.3	<1.0	16.7
—	160	223	295,000	285,000	7.5	12.8	6.0	88.0
—	118	189	150,000	140,000	30.0	45.0	<1.0	16.6

otic sac through the catheter. This was followed by the injection of a broad-spectrum antibiotic (usually 500 mg of ampicillin) via the same route. A test dose of 5 mg of $PGF_{2\alpha}$ was then injected, followed in five minutes by 25 mg of $PGF_{2\alpha}$, if no side effects occurred. The catheter was then removed and a dressing was applied to the puncture site.

Results

All patients were delivered within 24 hours of commencing the procedure (the mean induction-delivery interval was 13.2 hours). One patient (Case 3), who exhibited evidence of DIC and secondary hyperfibrinolysis, received augmentation of an intravenous infusion of oxytocin (5 Mu/min) for a period of four hours.

Only 4 of the 20 patients had received prenatal care. Fifteen fetal deaths presumably occurred during the third trimester. The estimated duration of fetal death was greater than 28 days in three patients (Cases 3, 7, and 11). In only 50% of cases could a probable cause of intrauterine death be determined.

The following complications could be attributed to the method of induction employed:

1. *Nausea and/or vomiting and/or diarrhea.* Three patients had these complications (Cases 5, 9, 17).
2. *Postpartum hemorrhage.* Two patients had postpartum hemorrhage (Cases 1 and 3). In Case 1, the hemorrhage was due to retention of part of the placenta following delivery. Case 3 had a postpartum hemorrhage due to persistent uterine atony and an associated coagulopathy.
3. *Retention of the placenta.* Two patients had partial or complete retention of their placentas. In Case 1, as described previously, partial retention of the placenta was associated with postpartum hemorrhage. In Case 15, no postpartum hemorrhage occurred, but manual removal of the placenta was necessary.
4. *Transient pyrexia.* Cases 14 and 18 experienced transient pyrexia (less than 38° C) which resolved spontaneously within 24 hours without prompting the use of antibiotics.

The results of plasma fibrinogen, serum FDP, and platelet count measurements, immediately prior to induction and at the time of delivery, follow: no statistically or clinically significant alteration occurred in plasma fibrinogen or blood platelet counts during induction and delivery, and in most patients FDP concentrations increased during labor. This is in consonance with the "physiologic" effect known to occur in labor.

Plasma hPL and progesterone concentrations prior to induction indicated a functional placenta in 12 of the 20 patients studied (Cases 1-6, 8, 9, 14, 15, 17 and 19).

Induction to abortion time was similar in those patients with a nonfunctional placenta (14.0 hours) to those with evidence of residual functional placenta (12.3 hours). The patient with DIC appeared to have a functional placenta. Concentrations and changes in fibrin degradation products were similar in patients with and without functional placentas (Table I).

Comment

In the past, difficulties associated with achieving successful induction of labor in patients with prolonged intrauterine death of the fetus led many obstetricians to favor an expectant approach to management. In most instances, the patient was given psychological support and was assured that labor would ultimately ensue. Apart from the mental anguish experienced by such patients, there was a risk that when a dead fetus was retained in utero for longer than 4 weeks, 25% would develop DIC.[11, 12] These considerations prompted efforts aimed at inducing labor in patients whose pregnancies were so complicated. The realization that amniotomy carries a high risk of aerobic and anaerobic infection[13] and that the infusion of oxytocin is often unsuccessful in pregnancies complicated by fetal death prompted attempts to sensitize the uterus with quinine and/or estrogens[14] prior to induction of labor with oxytocin. Although intra-amniotic hypertonic saline was advocated for the management of pregnancies complicated by fetal death, this method was associated with the development of severe DIC and hyper-natremia.

The intra-amniotic instillation of $PGF_{2\alpha}$ in combination with urea is not associated with an escalation of DIC. Neither does the induction-delivery interval appear to be influenced by the presence of residual functional placental tissue. The one patient who had DIC had the syndrome prior to induction. There were no significant changes in plasma fibrinogen concentrations, blood platelet counts, or serum FDP concentrations over the induction period. And there was no difference in the value of these blood coagulation parameters between the patients with or without evidence of functional residual placenta. The induction to abortion time, complications, and side effects were similar in patients with evidence of functional placenta and those without such evidence. The method, which requires only a single intra-amniotic instillation, appears to be both practicable and highly reliable.

As mentioned earlier, prostaglandins have effectively been administered via the intravenous, intrauterine extraovular, intra-amniotic, and vaginal routes.[3, 5–7] The intrauterine extraovular method is effective but is associated with a relatively high complication rate. This limits the clinical applicability of this method. Appropriate doses of intra-amniotic prostaglandin result in satisfactory abortion rates and a clinically acceptable incidence of side effects. However, the concomitant use of urea permits one to use a lower dose of $PGF_{2\alpha}$ and eliminates the need for repeated intra-amniotic instillations, while the same degree of effectiveness is achieved in association with a low complication rate. Although vaginal administration is convenient, absorption is inconsistent and overt vaginal bleeding often occurs. The convenience of the vaginal route of administration does, however, warrant further investigation into this method of management.

A special protective problem that may occur with the use of urea and prostaglandin $F_{2\alpha}$ in this setting is the occurrence of hypertonic injury when the urea is inadvertently injected into tissue such as the myometrium. This can be avoided by paying meticulous attention to suggested technique, i.e., withdrawal of amniotic fluid prior to injection of urea and prostaglandin and the injection of these agents via a correctly placed polythene catheter that will not be displaced by uterine contractions.

DIC and secondary hyperfibrinolysis have been shown to be associated with a degree of uterine atony that is relatively resistant to oxytocics and results in postpartum hemorrhage[16] (Case 3). Likewise, patients with severe abruptio placentae associated with serum FDP concentrations in excess of 320 μg/ml have been shown to experience severe antepartum uterine atony that is refractory to oxytocin infusion.[17]

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Sexual behavior and response in relation to complications of pregnancy

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A detailed written questionnaire survey of 155 puerperas is reviewed. Sexual and obstetric data were examined for possible associations leading to premature or low-birth-weight infants. Among 25 patients delivering premature infants (16 with babies weighing less than 2,500 grams), no significant association could be made between coitus, orgasm, and/or other sexual experiences and the proximity to the onset of labor. Orgasmic patients appeared to have a consistently lower percentage of early deliveries. No particular method of sexual gratification was unique except that masturbation was consistently associated with a lower risk of prematurity throughout various stages of gestation. Speculations are advanced to explain these observations. Sexual activity appears to be safe throughout pregnancy in almost all patients. Ruptured membranes on admission may be associated with recent sexual stimulation without orgasm. (AM. J. OBSTET. GYNECOL. 134:498, 1979.)

IT IS a prevalent opinion that sexual behavior and response during pregnancy may in some way be related to certain untoward gestational complications. Data to substantiate this opinion are scanty and inferential. As yet, no prospective study has been published which is designed to address and resolve this issue. Most standard texts and (we suspect) most physicians confronting these issues are silent or skeptical regarding the safety of normal sexual activity in pregnancy, particularly in the latter weeks or in situations where an increased risk of premature delivery is recognized.

Previous reports attempting to address this issue have dealt with the recognized association between orgasmic response and uterine contractility,[1] or have attempted to show heightened sexual behavior and response in patients ultimately delivering premature infants.[2] The matter of the association between sexual activity and spontaneous rupture of membranes has been suspected by many, but no reports attempting to resolve this issue have appeared.

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In an attempt to shed a little more light on this important but poorly explored area of human behavior, relevant portions of a large study recently completed on sexual behavior and pregnancy were reviewed. A highly detailed analysis of the study as a whole is in preparation and will be extensively reported later.

Material and methods

The study was conducted over a brief time period on the postpartum unit at the University of Colorado Medical Center in late 1976. An elaborate questionnaire was distributed to the patients in order to study many aspects of their personal and sexual lives before and during pregnancy. All patients were invited to participate in the study, and only those who were physically unable to contribute or who were non-English speaking were excluded. The questionnaire was explained to the patients and the terminology made clear to avoid confusions in interpretation. The patients were assured of anonymity and that they would not be questioned further regarding the particulars of their responses except if they wished further investigation. The questionnaire was administered by a female professional skilled in psychological techniques and interpersonal relationships. Obstetric data was added from the mothers' and babies' charts prior to removal of the identifying cover sheet. Results were then coded and subjected to statistical analysis.

A total of 190 questionnaires were distributed. Twenty-four patients declined to participate. Some of these patients discarded their questionnaires and

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others completed only nonsensitive portions. A total of 172 questionnaires were available for review at the conclusion of the study and, of these, 17 were sufficiently incomplete to preclude useful data analysis. The remaining 155 questionnaires were subjected to analysis.

The ages of the respondents varied widely. Of those studied, one was less than 16 years of age. Of the remainder, 61 were age 16 to 20, 56 were age 21 to 25, 33 were age 26 to 35, and 4 were over 35. A total of 97 (62.6%) listed their occupation as "housewife," 11 (7.1%) as "student," 18 (11.6%) as "full-time employed," 13 (8.4%) as "part-time employed," and 16 (10.3%) as "unemployed."

Fifty-one patients (32.9%) were in their first pregnancy. In addition, 78 (50.3%) had never experienced a prior viable birth.

Racial distribution of the population was as follows: black—14 (9.0%), Chicano (Mexican-American)—19 (12.3%), white—120 (77.4%), and "other"—2 (1.3%).

Forty-one (26.5%) listed their religion as Catholic, 2 (1.3%) as Jewish, 73 (47.1%) as Protestant, 27 (17.4%) as "no preference," and 10 (6.5%) as "other."

With regard to marital status, 117 (75.5%) described themselves as married, 18 (11.6%) as single, 7 (4.5%) as divorced or separated, and 13 (8.4%) as "common law" status.

By education background, 3 (1.9%) had received no more than an eighth grade education. One hundred twelve (72.3%) had completed some or all of a high school education, and 39 (25.2%) had been educated beyond the high school level.

In surveying the sexual status of the population, many aspects of sexual behavior and response before and during pregnancy were studied. Patients were asked to characterize the frequency of utilization of seven major sexual behavior patterns before pregnancy, during the first three months, during the middle of pregnancy, and during the last two months. These behavior patterns were: intercourse with simultaneous genital stimulation by the partner, intercourse with simultaneous self-stimulation, intercourse alone, noncoital genital stimulation by partner's hand, noncoital genital stimulation by partner's mouth or tongue, "other" noncoital genital stimulation, and masturbation (characterized as self-stimulation with partner absent, to mitigate negative responses to the emotionally charged terminology). Patients were asked to provide some response to the utilization of each technique from 0 to 100% of the times sexual stimulation occurred.

In addition to the above, patients were asked to indicate in each case whether or not orgasm occurred at least 50% of the times such stimulation was experienced. By this means, the frequency of orgasmic response to various techniques could be determined in addition to the frequency of utilization of various techniques before and throughout pregnancy.

Other relevant determinations subjected to analysis for the purposes of this report included the incidence of rupture of membranes prior to admission to the hospital (whether or not the patient was in labor), the time interval between the patient's last sexual experience and the onset of labor, the incidence of prematurity (defined as the birth of an infant determined to be less than 38 weeks gestational age), and the incidence of low-birth weight infants (less than 2,500 grams).

In order to determine the relative incidence of the production of perceptible uterine irritability by various sexual events, the patients were asked to characterize the association between uterine contractions at various stages of pregnancy and coitus with orgasm, coitus without orgasm, orgasm without associated coitus, and other sexual stimulation without orgasmic response. By this means, it was hoped that the relative contributions of coital stimulation, noncoital stimulation, and orgasm to the production of perceptible uterine activity could be ascertained.

All data derived were subjected to analysis through the Statistical Package for the Social Sciences, utilizing modified chi-square differentiations.

Results

Since some patients did not respond to each and every question asked, evaluation will be limited to those patients in whom a response was available. After careful analysis of the frequency of events among nonresponders it was determined to our satisfaction that missing responses, even were they to occur in incriminating categories, would not change the overall results or conclusions significantly.

A total of 13 patients (8.4%) had never been orgasmic. These patients will therefore be consistently included in the nonorgasm study group. The distributions of these patients were as follows: black—4/14, Chicano—2/19, white—7/119; Catholic—2/41, Protestant—7/73, "no preference"—4/27; age 16 to 20—10/61, age 21 to 25—2/55, age 26 to 35—1/33; married—8/123, unmarried—5/31; high school education—12/111, beyond high school—1/39. These differences were found not to be of major statistical significance and not important in relation to other data to be reported below.

Sex and onset of labor. Of the total population, 20 patients reported the onset of labor within 24 hours of their last sexual experience (regardless of its nature)

Table I. Correlation of events with time of labor onset after last sexual experience

	Interval			
	No data	*<24 hr.*	*>24 hr.*	*p*
Membranes on admission:				
Ruptured	5	8	34	NS
Unruptured	10	7	73	
Response, last experience:				
Orgasm	1	8	41	NS
No orgasm	14	11	63	
Gestational age at delivery (wk.):				
<38	3	7	15	<0.025
38+	7	13	92	
Birth weight (gm.):				
<2,500	2	4	10	NS
>2,500	14	16	98	

Table II. Association of ruptured membranes before labor, interval to labor onset, and habits and orgasmic response with last sexual experience

	Interval to labor onset		
Sexual experience	*<24 hr. (No.)*	*>24 hr. (No.)*	p_1
Coitus:			
Premature rupture	7	24	NS
No premature rupture	6	58	
No coitus:			
Premature rupture	1	10	NS
No premature rupture	1	15	
p_2	NS	NS	
Orgasm occurred:			
Premature rupture	0	17	<0.05
No premature rupture	8	24	
No orgasm occurred:			
Premature rupture	8	17	<0.005
No premature rupture	3	49	
p_2	<0.005	NS	

p_1 = Variables of interval to labor onset and ruptured membranes.

p_2 = Variables of habits or orgasmic response and ruptured membranes.

Of the remainder, 30 patients reported either no sexual experience within two months of delivery or did not respond to the question. One hundred four patients had had at least one sexual experience between 24 hours and 60 days from the onset of labor, and these were relatively uniformly distributed.

Since it seemed unreasonable to assume an association between sexual stimulation and the onset of labor if the interval exceeded 24 hours, the population was then studied in relation to labor onset before and after the 24 hour period. The response to the sexual stimulation last experienced was related to the time of labor onset as was the presence or absence of an association

Table III. Orgasmic response by stages of pregnancy, habits, and incidence of premature delivery (orgasmic women only)

	Stage of pregnancy and prematurity (%)		
Habits and response	*First third*	*Middle*	*Last 2 mo.*
Coitus with partner stimulation (No.):	(124)	(108)	(79)
Orgasm	10.7 } *	12.2	6.9
No orgasm	24.5 } *	16.9	22.0
Coitus with self-stimulation (No.):	(42)	(37)	(22)
Orgasm	14.3	11.1	12.5
No orgasm	32.1	21.4	42.9
Coitus alone (No.):	(87)	(82)	(61)
Orgasm	8.1 } b	17.6	18.7
No orgasm	24.0 } b	20.8	23.1
Hand stimulation (No.):	(100)	(37)	(67)
Orgasm	20.7	16.7	11.8 } b
No orgasm	18.3	15.9	18.0 } b
Oral stimulation (No.):	(85)	(66)	(48)
Orgasm	14.6	9.7	10.5
No orgasm	22.7	22.9	17.2
"Other" stimulation (No.):	(76)	(66)	(47)
Orgasm	12.5	0 } ‡	0
No orgasm	20.0	22.6 } ‡	23.1
Masturbation (No.):	(48)	(36)	(28)
Orgasm	8.7 } †	9.1 } †	11.1 } †
No orgasm	40.0 } †	42.9 } †	50.0 } †

b = borderline ($p > 0.05 < 0.10$).

*$p < 0.05$.

†$p < 0.025$.

‡$p < 0.005$.

with premature rupture of membranes (defined as rupture prior to hospital admission) and gestational age and weight at delivery. The results are shown in Table I.

It can be seen that there is no association between the interval between the last experience and the onset of labor and the status of the membranes on admission with the presence or absence of orgasmic response with that experience or with birthweight. An association is noted between the gestational age at delivery and the proximity of the last experience to labor onset. The significance of this will be discussed later.

Table II explores the association of these various events with each other. It can be seen from this display that (as shown by p_1) there is no statistical difference among those experiencing coitus and noncoital sexual stimulation and the incidence of premature membrane rupture among those experiencing labor onset before and after 24 hours. As shown by p_2, there is also no difference among those with labor onset within and after 24 hours and the incidence of ruptured membranes between those experiencing coitus and noncoital stimulation.

Table IV. Prematurity and fetal growth by sexual habits, last 2 months

	Gestational age (wk.)			*Birth weight (gm)*		
	<38 (No.)	*38+ (No.)*	*p*	*<2,500 (No.)*	*>2,500 (No.)*	*p*
Coitus with partner stimulation:						
Used	8	71	NS	8	77	NS
Not used	9	50		5	54	
Coitus with self-stimulation:						
Used	7	19	NS	4	22	NS
Not used	16	102		9	109	
Coitus alone:						
Used	13	52	NS	8	57	NS
Not used	10	69		5	74	
Hand stimulation alone:						
Used	13	59	NS	6	66	NS
Not used	11	62		8	65	
Oral stimulation alone:						
Used	8	43	NS	6	45	NS
Not used	15	78		7	86	
"Other" stimulation alone:						
Used	11	40	NS	6	46	NS
Not used	13	80		8	85	
Masturbation:						
Used	7	21	NS	4	24	NS
Not used	17	99		11	105	

As is also shown in Table II, there is a significant ($p < 0.05$) difference in the incidence of membrane rupture prior to admission among those experiencing orgasm during their last sexual exposure when such exposure occurred more than 24 hours prior to the onset of labor when compared with those experiencing onset less than 24 hours (there being no patient admitted with premature ruptured membranes and a sexual interval less than 24 hours who had experienced orgasm with that event). Among those who did *not* experience orgasm with their last experience, however, a significantly greater number ($p < 0.005$) were admitted with ruptured membranes if their last experience had been less than 24 hours prior to labor onset than those with stimulation occurring more than 24 hours before labor. In addition, among those who labored within 24 hours of their last experience, a significantly greater number ($p < 0.005$) were admitted with ruptured membranes if orgasm had *not* occurred than if it had. The difference among those with labor onset greater than 24 hours after their last experience was not significant.

When the population was studied by the presence or absence of a prior birth, no differences were noted in the incidences or significances of these various comparisons.

Among the total population, 34 patients claimed at some time to have prevented orgasm. Of these, 21 claimed this in the last two months due to: fear of hurting baby (8), fear of starting labor (2), told not to have sex or orgasm (7), orgasm was painful (5), "other" reasons (4).

Prematurity and sexual behavior. Since the population was given identical choices to describe various sexual techniques and response throughout various stages of pregnancy, it was possible to follow the trends of behavior and responsiveness throughout the various stages and to explore the possible association between these patterns and the production of a premature infant. Of the total population, 27 patients (17.4%) produced an infant assessed at less than 38 weeks gestational age. Data on 25 patients were complete enough for study. Utilizing this information, and studying only women with orgasmic performance in the past, the association between orgasm by various types of stimulation and the incidence of prematurity is shown in Table III.

It can be seen from this display that the incidence of the utilization of all techniques of stimulation declines throughout pregnancy. It will also be seen, however, that at all stages of pregnancy there is either no association between orgasmic response (>50% of the time) and the production of a premature infant or that when such association exists, the incidence is significantly lower among orgasmic than among nonorgasmic mothers. Although in most cases numbers are quite small, it is presumed that were there a consistent cause-and-effect relationship between orgasmic response and the production of premature labor, the differences demonstrated would at least have been in the nature of a

Table V. Prematurity and fetal growth by orgasmic response, last two months

	Gestational age (wk.)			*Birth weight (gm)*		
	<38 (No.)	*38+ (No.)*	*p*	*<2,500 (No.)*	*>2,500 (No.)*	*p*
Coitus with partner stimulation:						
Orgasm	2	27	NS	2	27	NS
No orgasm	11	39		5	45	
Coitus with self-stimulation:						
Orgasm	1	7	NS	0	8	NS
No orgasm	6	6		4	10	
Coitus alone:						
Orgasm	3	10	NS	3	10	NS
No orgasm	9	39		4	44	
Hand stimulation alone:						
Orgasm	2	15	0.08	1	16	NS
No orgasm	9	41		3	47	
Oral stimulation alone:						
Orgasm	2	17	NS	1	18	NS
No orgasm	5	24		4	25	
"Other" stimulation alone:						
Orgasm	0	8	NS	0	8	NS
No orgasm	9	30		4	35	
Masturbation:						
Orgasm	2	16	<0.025	1	17	0.08
No orgasm	5	5		3	7	

Table VI. Association of habits and response with perceived uterine contractions at various stages of pregnancy

Behavior and response	*Contractions noted (%)*			*None (%)*
	First 3 mo.	*Middle*	*Last 2 mo.*	
Coitus and orgasm	10.4	10.4	16.3	70.1
Coitus, no orgasm	2.0	9.0	13.5	78.1
Orgasm, no coitus	3.2	7.1	12.3	82.5
No orgasm, other stimulation	1.3	3.2	9.0	88.4

Approximate percentage contributions of various stimuli to uterine contractions in last two months, from data above: coitus, 4.5%; orgasm, 3.0%; sexual arousal, per se (includes natural uterine irritability, unknown quantity), 9.0%.

trend toward an association between orgasm and prematurity. If anything, the trend is clearly away from such an association. The percentages displayed are those of the incidence of prematurity within that patient group. Even such a potent stimulus as masturbation (presumably clitoral in most cases), which is acknowledged to produce the most intense physical response,[3] showed no association with prematurity. The relative decline in such behavior in the population was less than that of other techniques.

Table IV illustrates prematurity rates (in patient numbers) by sexual habits used in the last two months of pregnancy. It can be seen that there are no significant differences in incidences of prematurity as related to the utilization or nonutilization of the various techniques. Table V further explores orgasmic response in relation to these factors and their relationship to sexual habits. Again, no significant associations between orgasmic response and the production of premature infants can be seen, with the exception that a significantly greater percentage of patients who are orgasmic with masturbation were delivered of mature infants when compared with those delivered of premature infants. Incidentally noted, but not surprising to those understanding female sexuality, a significant percentage of women in the study engaged in masturbation without the achievement of orgasm. By standards traditionally applied to the male, some might find this surprising. Patients orgasmic with masturbation actually were delivered of a significantly greater number of term infants than were women not orgasmic by this method.

Sexual habits and response were also explored in relation to their possible association with the production of low-birth weight infants. Although this bears considerable relation to prematurity, a possible association between sexual response and the production of growth retardation is also implied. Table IV also illustrates the

relative numbers of patients delivering babies weighing less than 2,500 grams in relation to various sexual habits throughout pregnancy. It will be seen that there is no statistical difference in the incidence of the utilization of various techniques and birth weight by these two standards. Table V further illustrates a lack of association between orgasmic response and the production of low–birth weight infants, with a borderline significant association between orgasm with masturbation and ostensibly normally grown babies. There appears clearly to be no association established between sexual techniques, responsiveness, and apparent normal growth.

Sexual behavior and uterine contractility. Table VI illustrates patient responses to the inquiry regarding the association between sexual behavior and perceived uterine contractions. It can be seen that throughout pregnancy, coitus with orgasm was more often associated with perceived uterine contractions at various stages than with other stimuli. It will also be seen that in the last two months, the uterus appeared more intrinsically irritable to stimuli of all sorts. Since 9.0% of patients perceived uterine contractions in association with sexual stimulation other than coitus but without orgasmic response, this was felt to represent an association with sexual arousal in a nonspecific sense, and to include coincidental uterine irritability perceived by the patient as associated with this behavior. Utilizing this assumption and using the exclusion of either coitus or orgasm by the other descriptive categories, one can derive a tenuous mathematical presumption regarding the contribution of coitus, orgasm, and baseline sexual arousal (including intrinsic uterine irritability) upon the incidence of perceived uterine contractions among respondents in the last two months. These are shown also in Table VI. If these assumptions bear any relationship to fact, coitus would then appear to consitute a stronger stimulus to uterine contractions than orgasm.

When the population is viewed by age, prior pregnancies, and prior births, no significant differences in intrinsic uterine irritability by any of these factors were noted; in general, however, parous patients perceived a greater incidence of uterine irritability than nulliparous patients. Because of the design of this questionnaire, however, it was impossible to distinguish nonresponders from those who did not experience contractile responses.

Comment

Because of the small numbers involved in the study, it is not intended that persuasive conclusions be drawn from the information presented. The study, however, does not suffer from the same potential for criticism to which similar studies in the past might be subjected. The population was selected without regard to obstetric data and control subjects used were not retrospectively matched. No confrontation interviewing was used, and answers therefore are assumed to be fairly frank and honest.

Goodlin[4] has been a proponent of the concept that orgasmic response and premature labor may be linked. In a later retrospective study,[5] he attempted to support the concept by noting an increased frequency of orgasm among patients who were delivered of premature infants compared with those delivered at term. After recognizing that the two groups were in some ways not comparable, in that the premature group was shown to be at greatly increased risk on the basis of a priór preterm delivery incidence three times that of the control subjects, the authors concluded that the effects were "additive." This mathematical speculation is unsupported. Noting that orgasmic frequencies were higher "after 32 weeks gestation" in the group delivering prematurely, they failed to recognize that, *at the same stage,* similar rates might have been found among the control subjects. The choice of a study interval of 50 hours from orgasm to the onset of labor raises questions regarding the reasons for the choice of this unlikely number and what advantage it played in fostering the premise.

Wagner and associates[2] studied a group of patients delivering prematurely out of a larger study with a format similar to ours. The use of a small number of "matched" control subjects appeared to show a greater degree of orgasmic activity among the prematurely delivering mothers at all stages of pregnancy; but when compared with the entire population, the differences were minimal, and the population as a whole was far from representative, being primarily white, married, and privileged. In all studies, also, it is hard to know how much "heightened consciousness" may be operating among mothers of threatened premature newborn infants, because self-scrutiny as to possible connections between their behavior and the unfortunate outcome is common.

The information from this study fails to establish any convincing connection between sexual habits with or without orgasmic response and such adverse obstetric events as premature labor, premature rupture of membranes, or low–birth weight infants. Although a significant association exists between a last sexual experience less than 24 hours prior to labor onset and delivery of an infant less than 38 weeks' gestational age, no association can be established with orgasmic response and rupture of membranes. It is possible that what is displayed is the recognized greater frequency of

sexual activity in earlier gestation than is found at term. Also, orgasmic response was actually more frequent among those delivering at term. Although one cannot support any contentions based upon these data, were one to draw any conclusion from the information, one would be forced to observe that sexual activity with orgasmic satisfaction may be associated with a better pregnancy performance than the alternative. Unfortunately, there were not a sufficient number of patients who were not sexually active in the latter part of pregnancy to form an adequate group to study from this perspective. An association is also noted between ruptured membranes and recent sexual activity without orgasmic response.

Because of the fact that information relative to sexual behavior and response in early pregnancy was derived by patient recollection, the possibility for inaccuracies exists. It is felt that this cannot be resolved, except to say that with the size of the data base such inaccuracies should be statistically minimized. In addition, the incidence of spontaneous nocturnal orgasmic (REM sleep) events was not sought. Finally, the possible contribution of seminal prostaglandins to uterine irritability would seem unlikely, since there would be no reason to presume the lack of seminal deposition during vaginal coitus among a population pregnant, and Table VI displays no difference in irritability with coital behavior except in the factor of maternal orgasm. The specific incidence of coitus without intravaginal ejaculation, however, was not sought.

Although other data from this study not presented in detail in this report do show a decline in overall sexual activity, interest, orgasmic response, orgasmic intensity, and attitude toward sexual activity progressively throughout pregnancy, patients generally reported a very low incidence of a decline of positive feelings regarding sex or their partners as a result of this pregnancy. Sexual activity declined at a lesser rate than did the patient's interest in such activity, suggesting that most patients maintained a willingness to participate out of regard for the needs of their partners. Only a small number of patients reported a decline in their partner's interest that was in excess of their own, and these patients generally increased masturbatory activity, apparently in compensation. These factors suggested a relatively low level of physical and emotional frustration in the population in relation to opportunities available. It will be interesting to study the incidence of premature labor arising in patients presumably oppressed by unrequited sexual frustration, since some authorities feel that premature labor may be more frequent among patients under stress. Based upon all these presently unsupportable presumptions, it may be surmised that, in the absence of adequate sexual satisfaction in the presence of need, patients might be more predisposed to premature labor than those engaged in regular, satisfying sexual relationships. These presumptions will be explored in the larger analysis of the study now in preparation.

Finally, miscellaneous observations regarding sexual behavior and response at various stages of pregnancy failed to establish a trend of events leading to premature delivery. The comparative use of anesthesia was not related to sexual factors. Despite the slight increase in the number of patients of low parity among the nonorgasmic women, analysis of variance showed no differences in the lengths of the first and second stages of labor among orgasmic versus nonorgasmic women. A more detailed assessment of the possibility that sexual behavior and response may determine labor and delivery performance will be forthcoming in the larger study analysis at a later date.

In summary, based on the information presented here, we would conclude that normal sexual activity has no demonstrated major adverse influence on gestation, and that, in the absence of obvious complications (such as bleeding, ruptured membranes, or threatened premature labor), there exists no contraindication to the pursuit of normal sexual activity throughout pregnancy. Orgasmic women appear, if anything, to be advantaged. Since recommendations against sexual activity, except in addressing a risk that the patient acknowledges or has previously experienced, are rarely followed, and since sexual proscription may impose additional stresses on patient-partner relationships already drawn taut, it would seem advisable that restrictions not be suggested without just cause. In addition, it should be the physician's responsibility to review this area with the couple and to provide them with helpful observations regarding problems in physical and mental adjustments to be faced in connection with sexual behavior in pregnancy. The ease and comfort with which a given physician approaches this area may serve to establish early in the professional relationship a meaningful dialogue for the identification of relationship dysfunctions which later arise. The obstetrician is in an unique position as a potential case-finder in marital discord, and pregnancy is a window on the strengths and weaknesses of the entire relationship. To fail to recognize and respond to such opportunities in a perceptive and professional way relegates the practitioner to the status of an obstetric technician.

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The efficacy of prophylactic antibiotics in cesarean section

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The objective of this investigation was to determine the effectiveness of cefazolin-cephalothin administration as a prophylactic regime in patients undergoing cesarean section. The study was to randomized, double-blind, placebo-controlled investigation. Cefazolin, 1.0 gm, or placebo was administered intramuscularly on call to the operating room, and cephalothin, 2.0 gm, or placebo was administered intravenously at 6, 12, and 24 hours postoperatively. Ninety-five patients were included in the study with 49 in the placebo group and 46 in the drug group. Nineteen patients developed 28 infections in the placebo group while eight patients developed eight infections in the drug group ($P = <0.05$). Eight patients in the placebo group developed infections at two or more sites whereas no patient in the drug-treated group developed multiple infections. No infant developed infection and no overgrowth of bacteria occurred. This study supports the concept of preoperative antibiotic administration being beneficial to the obstetric patient. (AM. J. OBSTET. GYNECOL. 134:506, 1979.)

THE EFFICACY and safety of the use of preoperative antibiotics in patients undergoing cesarean section has been studied for more than ten years with the first publication in 1968.[1] However, the scientific basis for the rational use of preoperative antibiotics was proposed in an earlier study by Burke.[2] Unfortunately the principles developed by Burke for preoperative antibiotics were ignored to some degree in subsequent studies. Mead[3] has summarized nine publications since 1969 concerning preoperative antibiotics in patients undergoing cesarean section. This summary indicated a febrile morbidity rate of 51% and a pelvic or wound infection rate of 30% in patients receiving a placebo, whereas the patients receiving the preoperative antibiotic had a febrile morbidity rate of 21% and a pelvic or wound infection rate of 11%. In spite of these data Mead[3] cautioned against the use of chemoprophylaxis in cesarean section.

The objectives of this investigation were to evaluate the safety and effectiveness of cefazolin-cephalothin administration as a prophylactic regimen in patients undergoing cesarean section.

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Material and methods

This study included patients who were admitted to Duke University Medical Center for repeat cesarean section or who developed a need for cesarean section while in labor. The study was a prospective randomized, double-blind, placebo-controlled investigation. Patients who demonstrated evidence of clinical infection had ruptured membranes of greater than 12 hours on admission, had received antibiotic therapy during the 48 hours period prior to surgery, or who demonstrated renal or hepatic disease were excluded from investigation. The patients were administered cefazolin,* 1.0 gm, or placebo intramuscularly on call to the operating room and cephalothin,† 2.0 gm, or placebo intravenously at 6, 12, and 24 hours after the first antibiotic or placebo drug.

Preoperatively and on the third postoperative day all patients were evaluated by complete blood count urinalysis, and blood urea nitrogen.

All patients had a five-minute preoperative scrub with providine iodine as a surgical scrub.

The evaluation of the patients receiving the active drug and placebo was based on illness, serious infections, wound healing, and the number of postop-

*Kefzol, supplied by Eli Lilly & Co., Indianapolis, Indiana.
†Keflin, supplied by Eli Lilly & Co.

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erative days in the hospital. Illness was defined as a temperature elevation of 38.0° C or greater on any two days excluding the first 24 postoperative hours or other signs of obvious infection. A wound infection was diagnosed when either cellulitis extending greater than 2 cm from the line of incision, purulent exudate in the subcutaneous or subfascial planes, intraperitoneal abscess, or peritonitis was present. Serious infections included wound infections, endometritis, parametritis, pelvic cellulitis, pelvic abscess, septicemia, and septic thrombophlebitis.

The drug and placebo groups were also evaluated by the effect on the bacterial flora of the infant. The first ten infants delivered were evaluated for bacterial overgrowth by comparing the bacterial flora obtained from the external auditory canal and distal nares immediately upon delivery and upon discharge from the nursery.

Cefazolin concentrations were determined from maternal serum, umbilical cord serum, and amniotic fluid obtained at the time of delivery.

Patients who were determined to be febrile or who had obvious signs of infection were evaluated with cultures from indicated sites of infection including blood, endometrial cavity, urine, and wound. Appropriate therapy was subsequently instituted. The code pertaining to the patient's medication was broken if requested by the attending physician.

Cultures of the endometrium were taken for aerobic and anaerobic organisms after insertion of a sterile speculum and cleansing of the cervix with a sterile dry sponge. A sterile swab was inserted into the endometrium and placed in an anaerobic specimen collector.* The swab was streaked on 5% blood agar, 5% sheep blood agar, and solid agar with phenyl ethyl alcohol and vancomycin-kanamycin added and placed in an anaerobic chamber at 37° C. The swab was also streaked on chocolate agar, 5% sheep blood agar, MacConkey's agar, and solid agar with colistin–nalidixic acid. The swab was placed in a chopped meat–carbohydrate broth. The aerobic cultures were incubated at 37° C.

Aerobic cultures were examined at 18 and 72 hours of incubation. Identification was carried out according to standard techniques.[4]

Anaerobic cultures were examined daily. At 72 hours of incubation, colonies were inoculated to chopped meat–carbohydrate broth. After an additional 72 hours they were used to innoculate anaerobic API strips† and for gas chromatography. The Virginia Polytechnic Institute Manual was used as reference for anaerobic bacteria.[5]

*Anaerobic Specimen Collector, Becton-Dickinson, Inc.
†Analytab Products Inc., Rutherford, North Carolina.

Table I. Number of patients infected and total number of infections in drug and placebo groups

	Drug group	*Placebo group*	
Patients in groups	46	49	
Patients infected	8	20	
% Patients infected	17.4	40.8	$p = <0.05$
Total no. of infections	8	28	$p = <0.01$

Table II. Site of postoperative infection in drug and placebo groups

Infection	*Study groups*	
	Drug	*Placebo*
Endometritis	5	7
Wound	1	1
Pulmonary	1	0
Urinary tract	1	2
Urinary tract and wound	0	1
Urinary tract and endometritis	0	3
Wound and endometritis	0	1
Septicemia and endometritis	0	2
Septicemia, endometritis, and wound	0	1
Septicemia	0	1
Pelvic cellulitis	0	1
	8	20

Results

There were no significant differences in the clinical characteristics of age, racial distribution, parity, number of catheterizations, or length of time of indwelling catheter between the two groups. Analysis of the results of the complete blood count, urinalysis, and blood urea nitrogen in the two groups showed no differences. In addition minor side effects such as a rash or pruritus or major reactions such as anaphylaxis were not observed.

Ninety-five patients were included in the study with 49 in the placebo group and 46 in the cefazolin-cephalothin group. Twenty of the 49 patients (40.8%) in the placebo group developed at least one postoperative infection while 8 of 46 (17.4%) of patients in the drug group became infected. The group of 20 patients receiving the placebo who became infected had 28 diagnosed infections while only eight infections occurred in the antibiotic-treated group (Table I).

The type and site of the infections which were diagnosed showed significant differences. These are listed in Table II. Eight patients in the placebo group had infections at two or more sites while no patient in the drug group developed multiple infections.

The bacterial organism and site of culture is presented in Table III. The pathogenic organisms in 9 of

Table III. Bacteria isolated from drug and placebo groups

Infection and/or site	*Drug*	*Placebo*
Endometritis (E)	1. *Enterobacter cloacae* 2. Anaerobic gram-positive rods 3. *Proteus mirabilis* and *Bacteroides fragilis* 4. *Bacteroides fragilis* and *Gaffkya sp.* 5. *Bacteroides fragilis* and *Peptococcus* sp.	1. Beta-hemolytic streptococcus: *E. Coli* 2. *Clostridium* sp., *Peptococcus* sp., *Bacteroides* sp. 3. *Bacteroides* sp. 4. Anaerobic gram-positive and-negative 5. Beta-hemolytic streptococcus 6. Beta-hemolytic streptococcus 7. No pathogen identified
Wound (W)	1. No organism cultured	1. *Peptococcus* sp., *Propionibacterium* sp.
Pulmonary	1. No organism cultured	None
Urinary tract (UT)	1. *Micrococcus aureus*	1. *E. coli* 2. No pathogen identified
Urinary tract (UT) and wound (W)	None	1. UT = *E. coli* W = not identified
Urinary tract (UT) and endometritis (E)	None	1. UT = *E. Coli* E = Alpha-hemolytic streptococcus 2. UT = *Proteus mirabilis* E = *Bacteroides* sp. 3. UT = *E. coli* E = *Peptostreptococcus* sp.
Wound (W) and endometritis (E)	None	1. E = Gram-positive anaerobic cocci W = K. *Pneumoniae*
Septicemia and endometritis	None	1. S = *Cl. perfringens* E = *Cl. perfringens: Bacteroides* sp. 2. S = *S. Aureus* E = Anaerobic gram-positive cocci
Septicemia, endometritis, and wound:	None	1. S = Anaerobic streptococci E = *Bacteroides* sp. W = Not cultured
Septicemia	None	1. Anaerobic gram-positive coccus
Pelvic cellulitis	None	1. *Bacteroides* sp.

Table IV. Length of hospital stay

	Study groups	
	Cefazolin (46)	*Placebo (49)*
Whole group	7.98 ± 1.54*	8.39 ± 1.91
Infected patients	9.50 ± 2.22	9.11 ± 2.56
No infection	7.56 ± 0.97	7.93 ± 1.20

*Standard deviation.

14 (64.4%) of placebo group patients and four of five (80%) antibiotic group patients developing endometritis were anaerobic bacteria. Anaerobic organisms were responsible for septicemia in three of four (75%) patients in the placebo group.

The average length of postoperative hospital stay was used as a measure of comparison of the two groups. No significant differences were noted (Table IV).

No differences were present in the patient groups when length of surgery or length of time from onset of surgery to delivery of the infant were compared. As the time interval between the administration of cefazolin and delivery increased the infection rate decreased (Table V).

No infant developed a superinfection and in no infant did the administration of the preoperative antibiotic interfere with routine pediatric cultures or assessment. The ten infants who were cultured upon delivery and discharge from the nursery showed no difference in bacterial flora.

The influence of primary versus repeat cesarean section and socioeconomic status is shown in Table VI. When infectious illness of primary versus repeat cesarean section was compared, no significant differences were observed in those patients receiving the prophylactic antibiotic (16.0% versus 19.0%) or the placebo (43.3% versus 36.8%).

The concentrations of cefazolin in maternal blood, cord blood, and amniotic fluid at the time of delivery and the length of time from administration of the drug to delivery of the infant is listed in Table VII. The concentration of cefazolin in maternal blood at 60 minutes varied from 30 to 60 μg/ml while cord blood concentrations were less than 25% of the maternal con-

Table V. Time of drug and length of surgery in relation to infection

Time interval	Drug group			Placebo group		
	Min.	Range	S.D.	Min.	Range	S.D.
Cefazolin to delivery	66.7	21-157	37.1			
Length of surgery	87.3	40-225	33.3	86.4	35-170	28.9
Start of surgery to delivery	11.3	3-34	6.6	13.3	2-43	7.6
Cefazolin to delivery in patients who developed infection	30 min.	1/4	(25.0%)			
	30-60 min.	5/23	(21.7%)			
	60 min.	2/19	(10.5%)			
		8/46				

Table VI. Infection as related to cesarean section and socioeconomic status

	Group			Infections			
	No.	Drug	Placebo	Drug	%	Placebo	%
Primary cesarean section	55	25	30	4/25	16.0	13/30	43.3
Repeat cesarean section	40	21	19	4/21	19.0	7/19	36.8
	95	46	49	8/46	17.4	20.49	40.8
Private	39	21	18	3/21	14.3	4/18	22.2
Nonprivate	56	25	31	5/25	20.0	16/31	51.6
	95	46	49	8/46	17.4	20/49	40.8

Table VII. Cefazolin concentrations (μg/ml)

Patient	Drug → DEL	O → DEL	Maternal blood	Cord blood	Amniotic fluid
8	NA	NA	35.0	2.0	0.5
11	28	4	35.0	16.0	0.6
12	155	20	40.0	16.1	NA
20	36	16	54.0	20.8	3.5
22	32	7	29.5	Neg.	Neg.
25	122	17	60.0	21.5	1.3
27	95	10	70.0	18.4	Neg.
32	60	5	30.3	2.4	Neg.
34	54	3	60.0	16.0	Neg.
35	48	3	45.0	8.4	0.3
37	102	7	30.0	6.8	Neg.
58	48	13	45.0	11.9	Neg.
78	45	15	56.0	17.0	Neg.
79	47	7	15.5	1.4	Neg.
91	87	7	40.0	NS	Neg.
99	48	13	36.0	1.6	0.7
103	29	4	27.5	3.8	1.7

DEL = Delivery; O = onset of operation; NA = not available.

centration and the amniotic fluid concentrations were extremely low or negative.

Comment

The prevention of serious postoperative infections in patients undergoing cesarean section is of increasing concern. As obstetricians have become more concerned with the infant outcome, the cesarean section rate in this country has doubled. Serious bacterial infections such as wound infections, endometritis, parametritis, pelvic cellulitis, pelvic abscess, septicemia, and septic thrombophlebitis need to be differentiated from noninfectious febrile illness due to atelectasis or drug reactions. The prevention of urinary tract and pulmonary infections by prophylactic antibiotics does not have rational scientific basis. Six of the eight patients in the drug-treated group developed infections which could be considered serious whereas 18 of 20 patients in the placebo group developed serious infections. Therefore 6 of 46 (13.0%) patients who received preoperative antibiotics and 18 of 49 (36.8%) patients who received a placebo developed serious postoperative infections. The presence of four patients who developed septicemia in the placebo group is alarming but no instance of septicemia occurred in the antibiotic group.

The timing of the administration of the prophylactic

Table VIII. Cefazolin prophylactic study—cesarean section: Postoperative antibiotics

Drug group		*Placebo group*	
Ampicillin	96.0 gm	Ampicillin	223.0 gm
Kanamycin	9.5 gm	Kanamycin	26.1 gm
Penicillin G	136.2 mg	Penicillin G	100 mg
Macrodantin	3.5 gm	Macrodantin	2.2 gm
Sulfisoxazole	30.0 gm	Sulfisoxazole	41.0 gm
		Cefazolin	38.8 gm
		Cephalothin	33.0 gm
		Clindamycin	45.0 gm
		Cephalexin	47.5 gm

antibiotic seems to be of a critical nature. Burke[2] has shown that if the antibiotic is administered subsequent to the arrival of the bacteria in the operative site the patient will not benefit. It is seen that the most appropriate length of time from antibiotic administration to delivery is less than one hour (Table V). This would be consistent with excellent antibiotic concentrations in maternal serum at the time of delivery (Table VIII). Most other studies which use prophylactic antibiotics in cesarean section have not measured antibiotic concentrations,[1, 6–10] but Weinstein and associates[11] measured placental transfer of clindamycin and Gentamicin when they were used in a prophylactic regimen. In a companion article Gibbs and Weinstein[12] found clindamycin-gentamicin to be no more effective than a regimen of ampicillin-kanamycin.

Criticism has been forwarded that the use of prophylactic antibiotics markedly increases the total amount of antibiotics patients will receive. Ledger and colleagues[13] showed that patients in their placebo group received considerably more antibiotics and this is also seen for this study (Table VIII).

Prolonged rupture of membranes (PRM) prior to delivery is thought to increase the maternal morbidity rate. Gibbs and colleagues[8] showed prophylactic antibiotics to be effective whether or not membranes were ruptured. In the present study patients were specially excluded if membranes were ruptured more than 12 hours prior to admission. This exclusion was deemed to be necessary because at some time after 12 hours of PRM, chorioamnionitis and endometritis will develop and therapeutic antibiotics should then be used rather than a prophylactic regimen. Patients manifesting frank chorioamnionitis should be treated with full-dose Penicillin or cephalosporin plus an aminoglycoside and clindamycin. The impact of antibiotic therapy in patients with prolonged premature rupture of membranes is beyond the scope of this research. Four patients developed the need for cesarean section after admission with PRM more than 12 hours and were included in the study. Two patients were treated in each group but none of the four developed an infection. Sixteen patients had PRM less than 12 hours with eight in each group. Three infections occurred in each of the drug and placebo groups.

The endometrial cultures were obtained by passage of a sterile swab through a cleansed cervix. It is recognized this is not a totally satisfactory method for obtaining a culture from the endometrium; however, a bacteriologically sterile technique is unavailable at this time.

This study shows a significant decrease in the incidence of all infections and in the incidence of serious infections when a prophylactic regimen of cefazolin-cephalothin was used. No adverse effects to mother or infant due to the drugs were observed. Cultures of the infant at the time of delivery and discharge from the nursery showed no difference whether or not the mother received an antibiotic. The choice of cefazolin seemed to be excellent as a preoperative antibiotic because only small amounts were found in umbilical cord serum and negligible amounts were present in amniotic fluid. This is probably due to the high protein binding of cefazolin.

This study supports the concept of preoperative administration of an effective antibiotic in high dosage for a short period of time as being beneficial to the obstetric patient undergoing cesarean section.

The drugs were provided by Eli Lilly & Co., Indianapolis, Indiana.

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Abnormalities among offspring of oral and nonoral contraceptive users

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An analysis of 223 children born between 1961 and 1965 to 5,465 women in a controlled experiment at the University of Puerto Rico School of Medicine, regarding the use of oral and nonoral contraceptives, failed to reveal any statistical differences in birth weight and physical abnormalities between the two contraceptive groups. The mean birth weight for the oral group was 7 pounds, 4.1 ounces, whereas for the nonoral group it was 7 pounds, 5.4 ounces. Abnormal physical findings were 10.7% for the oral group and 16.7% for the nonoral group. A comparison is also made between the two groups with respect to incidence of abnormalities by socioeconomic class and by sex of the child, as well as by the number of pregnancies and age of the mother. No significant differences were noted between the groups as an indication of the effect of oral contraceptives. (AM. J. OBSTET. GYNECOL. 134:512, 1979.)

SINCE the development of oral contraceptives, many questions have appeared, opening the way to research and debate between scientists and lay people. Many sectors of our society wonder about their possible effects on women and their offspring. Suspicions regarding a potentially teratogenic role for "the pill" have been voiced for several years but reports have been conflicting, as may be observed in reviewing the literature up to 1976.

At the University of Puerto Rico Medical Sciences Campus, a controlled experiment is being carried out with over 10,000 women, about half of them using oral contraceptives and the remaining using nonoral (vaginal) methods. Several parameters have been studied since the beginning of the experiment in 1961 and the results of the comparison between the oral and control groups have been published.[1-3]

The present report deals with the description of some findings of a study with regard to the presence of some congenital abnormalities in children whose mothers have been using two kinds of contraceptive methods, oral and nonoral. Birth weights of the children from the two groups of women are compared. The variables are also compared by sex of the child and socioeconomic condition of the mother as well as by age at the time of delivery and number of pregnancies of the mother.

Material and methods

The subjects of this study were offspring of women belonging to the University of Puerto Rico Maternal Health Study Program which was designed in 1961 to study the incidence of genital and breast cancer in women who were using progestational agents. Women admitted to the study program met basic minimum qualifications such as: age 21 to 39 years, at least one normal pregnancy, and no prior use of oral contraceptives or of intrauterine contraceptive devices (IUDs). Each candidate before admission to the program agreed to use the contraceptive to be prescribed.

Once a woman was found to be eligible and prior to her physical examination, she was assigned at random to the experimental* (oral contraceptive) or control group (vaginal contraceptive), which she was to follow throughout the experiment.

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*The oral contraceptive group used norethynodrel, 5 mg, and mestranol, 0.075 mg (Enovid, G. D. Searle & Co., Chicago, Illinois). The total steroid dosage was 5.75 mg per tablet.

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The 5,465 women of the present study were admitted to one of the clinics in the project between 1961 and 1965. With randomization procedure 2,741 women (50.16%) were assigned to the oral contraceptive group and 2,724 (49.34%) were assigned to the control group. A comparison of several socioeconomic characteristics such as age, education, family income, occupation, parity, etc., of the randomly assigned subjects to our two groups showed that both groups were almost identical and therefore comparable.[3]

The next step was to identify the mothers who had offspring after admission to the study. These were mostly voluntary pregnancies, since there were no cases of contraceptive failure among either of the groups. During the period 1961 to 1965, 229 children were born to these women. Of these 229 children, 223 were included in the study; the remaining six subjects had moved with their families to other communities and therefore were lost to follow-up. Of the 223 children included in the analysis, 210 were alive and 13 had died at the time of the study.

The subjects of the present study (223) were distributed as follows: 103 children (44 boys and 59 girls) were in the group whose mothers used oral contraceptives and 120 (65 boys and 55 girls) were in that of women using nonoral contraceptives. The average age at the time of study was 6.1 years for the 96 living children of the study group and 6.2 years for the 114 living children of the control group.

Each living child was referred to a pediatrician who performed a complete physical examination and recorded a detailed history including birth weight. For the dead children the data were obtained from autopsy records or death certificates. A comparison between groups was made by variables of the child and mother using appropriate statistical analysis. A 5% level of probability was used as the criterion for significance tests.

Results

Birth weight. From the two groups (103 oral and 120 nonoral) only three birth weights for oral and one for nonoral groups were not available for the birth weight study. Thus the analysis included 100 subjects for the oral group and 119 for the nonoral group. The mean weight at birth for the oral group was 7 pounds, 4.1 ounces, and for the nonoral group it was 7 pounds, 5.4 ounces, with a standard deviation of 24.6 ounces for the oral group and 24.3 ounces for the nonoral group (Table I). From these values it can be observed that the difference (1.32 ounces) between the mean birth weights of the two groups is not significant at the 5% level as indicated by the t test.

Abnormal physical findings. Table II shows the number of abnormalities found during physical examination of children in both groups. In the oral group 11 abnormalities were found among the 103 children whereas in the nonoral group 20 of 120 children showed some abnormalities. The percentages of abnormalities were 10.7% for the oral group and 16.7% for the nonoral group. The total chi-square value is 1.660 with one degree of freedom, which indicates that the difference between observed frequency and expected frequency is not significant at the 5% level, that is, the difference between the percentages of abnormal cases in both groups could be considered to have occurred by chance and therefore the incidence is almost the same in both. On an average it was 13.9%. A list of the different abnormalities found in each case study is given in Table III.

Table IV shows the abnormal physical findings by socioeconomic groups according to standards previously established for the experimental subjects.[3] Data for 210 children were available for this variable. In the upper class no abnormalities were found in either group. The middle-class group included 10 cases from the oral group and 14 cases from the nonoral group, and for the low class one abnormal case was found in the oral group and three in the nonoral group. The percentages of abnormalities for the middle class thus were 13.7% and 15.1% for the oral and nonoral groups,

Table I. Test of significance of difference between mean birth weights of children born to mothers of the oral and nonoral contraceptive groups

	Oral group	*Nonoral group*
No. of children	100*	119*
Mean weight at birth	116.1 ounces (7 pounds, 4.1 ounces)	117.4 ounces (7 pounds, 5.4 ounces)
SD	24.6 ounces	24.3 ounces

Difference between means not significant at 5% level (t = 0.40).

*Birth weights of three children in oral and one child in nonoral group were not available.

Table II. Comparison of number of children with abnormalities observed between offspring of oral and nonoral groups

Group	*Oral*	*Nonoral*	*Total*
Normal	92	100	192
Abnormal	11	20	31
Total	103	120	223
Abnormal (%) (average 13.9)	10.7	16.7	

$\chi^2 = 1.660$ with one degree of freedom. Not significant at 5% level.

Table III. List of abnormal physical findings in study group

Oral contraceptive group	*No. of cases*	*Nonoral contraceptive group*	*No. of cases*
		Left inguinal hernia	1
Congenital defect of nose	1	Epilepsy*	1
High-arched leg	1	Vitiligo at neck*	1
Grade I systolic murmur	1	Grade 1 systolic murmur*†	9
Nevus of skin*†	1	Hypoplastic mandible	1
Seizures by history*†	1	Focomelia*	1
Deformed right side of chest*†	1	Micrognatia*	1
Abundant body hair*†	1	Microglossia*	1
Hairy pigmented nevi at neck	1	High-arched palate*	1
Earlobe folded forward	1	Right tibial torsion	1
Umbilical hernia	1	Juvenile premature ventricular contractions	1
Undescended testis	1	Right undescended testis*†	1
Genu varum right leg	1	Speech defect	1
Pectus excavatum	1	Endocardial fibroelastosis	1
		Anencephalic monster	1
		Cleft palate*†	1
		Inperforate anus*†	1

*Abnormal findings in the same patient.
†Abnormal findings in the same patient.

Table IV. Number of children with abnormalities by socioeconomic level for oral and nonoral groups

Socio-economic level	*Oral*		*Nonoral*		*Total*	*Significance of difference*
	Normal	*Abnormal*	*Normal*	*Abnormal*		
High	5	0	4	0	9	
Middle	63	10	79	14	166	
Low	17	1	14	3	35	
Total	85	11	97	17	210*	
Abnormal (%), high class	–	–	–	–	–	NS at 5%
Abnormal (%), middle class	–	13.7	–	15.1	14.5 (average)	NS at 5%
Abnormal (%), low class	–	5.6	–	17.6	11.4 (average)	NS at 5%

$\Sigma\chi^2 = 3.510$ with 6 degrees of freedom—not significant at 5% level; NS = Not significant.
*For 13 subjects, the socioeconomic level of the mother could not be obtained.

respectively. The low class indicated 5.6% for the oral and 17.6% for the nonoral group. The total chi square for the differences between observed and expected frequencies was 3.510 with six degrees of freedom. The difference between observed frequency and expected frequency is therefore not significant at the 5% level in this case either. Thus the percentages in both cases are considered almost the same with an average of 0.% for upper class, 14.5% for middle class, and 11.4% for low class. The difference between these three groups at individual socioeconomic classes was also insignificant at the 5% level as indicated in Table IV.

A comparison between groups was also made with reference to sex. In the oral and nonoral groups there were 10 and 13 cases, respectively, with abnormal physical findings in the boys and one and seven cases for the girls. The percentage of abnormal boys in the oral group was 21.7% whereas for the nonoral group it was 20.0%. The difference, however, is not significant at the 5% level, as indicated in Table V. The percentage of abnormal girls in the oral group was 1.8%, whereas for the nonoral group it was 12.7% which, as indicated in Table V, is a significant difference at the same level.

In the two groups under study the distribution of mothers by age, as presented in Table VI, showed that the average age of the mothers of the 103 children in the oral group was 31.5 years while that of the mothers of the 120 children in the nonoral group was 32.0 years. The difference between the two averages is not significant.

The mean ages of mothers of the normal and abnormal children in the two groups also failed to show any statistical difference, indicating that age is not an

Table V. Number of children with abnormalities by sex for oral and nonoral groups

Sex of child	Oral		Nonoral		Total	Significance of difference
	Normal	Abnormal	Normal	Abnormal		
Male	36	10	52	13	111	
Female	56	1	48	7	112	
Total	92	11	100	20	223	
Abnormal (%), males	21.7		20.0		20.7 (average)	NS at 5%
Abnormal (%), females	1.8		12.7		7.1 (average)	Significant at 5%

$\Sigma\chi^2 = 13.64$ with 3 degrees of freedom—significant at 1% level

Table VI. Age distribution of mothers of normal and abnormal children in oral and nonoral groups

Age group (yr.)	Oral group			Nonoral group		
	Normal (%)	Abnormal (%)	Total (%)	Normal (%)	Abnormal (%)	Total (%)
25-29	37.0	45.5	37.9	37.0	40.0	37.5
30-34	39.1	36.4	38.8	28.0	30.0	28.3
35-39	20.6	9.1	19.4	30.0	25.0	21.2
40 and over	3.3	9.1	3.9	5.0	5.0	5.0
Total %	100.0	100.0	100.0	100.0	100.0	100.0
No.	92	11	103	100	20	120
Average age (yr.)	31.5	31.6	31.5	32.1	31.8	32.0

Common standard error = 4.314 (based on 219 degrees of freedom in the analysis of variance).

Table VII. Distribution of number of pregnancies of mothers of normal and abnormal children in the oral and nonoral groups

No. of pregnancies as of childbirth	Oral group			Nonoral group		
	Normal (%)	Abnormal (%)	Total (%)	Normal (%)	Abnormal (%)	Total (%)
2	0.0	9.1	1.0	4.0	0.0	3.3
3	14.1	9.1	13.6	13.0	15.0	13.3
4	18.5	9.1	17.5	16.0	25.0	17.5
5	20.6	27.2	21.4	14.0	0.0	11.7
6	12.0	9.1	11.6	14.0	15.0	14.2
7	12.0	18.2	12.6	9.0	10.0	9.2
8 or more	22.8	18.2	22.3	30.0	35.0	30.8
Total %	100.00	100.0	100.0	100.0	100.0	100.0
Total No.	92*	11*	103	100†	20*	120

*$\chi^2 = 9.43$ (not significant at 5% level).
†$\chi^2 = 4.59$ (not significant at 5% level).

important factor affecting the children of our study with any abnormality.

The data were also analyzed for the 223 children as to their position in the family raised by the mother. The rank or the position thus was equivalent to the number of pregnancies incurred by the mother as of this childbirth. Table VII shows the data for the two groups, oral and nonoral, of the mothers of these children. It was observed that the distribution of the mothers according to the number of pregnancies was fairly similar in both groups. When the number of pregnancies of mothers in cases of the normal and abnormal children is compared, the distribution in either group is similar, as indicated by the chi-aquare test. Thus the observed frequencies, although apparently different, are not statistically different from their respective expected value.

Table VIII shows the 13 dead children with their ages at the time of death and the cause of death as reported in autopsies and death certificates. As can be seen clearly none of the deaths can be attributed to the use of oral contraceptives. Moreover, the three dead children who demonstrated congenital anomalies (vertebral, anal, cardiac, tracheal, esophageal, renal, and

Table VIII. Age and cause of death of 13 children in study groups

Patient	*Age*	*Cause of death*
Oral:		
H. M. R. V.	45 days	Pneumonia, acute gastroenteritis, dehydration
N. M. L.	4 yr.	Acute intoxication with organic phosphorus
C. W. C. G.	2½ mo.	Pneumonia, acute gastroenteritis, dehydration
Baby of L. R. M.	SB	Abruptio placentae after trauma, no anomalies
Baby of P. D. A.	SB	Premature labor, intrauterine asphyxia, no anomalies
L. M. F. E.	1 yr.	Pneumonia with asphyxia secondary to aspiration of ascaris
Baby of B. L. B.		Unknown
Nonoral:		
R. R. M.	2 yr.	Multiple body trauma, congenital heart disease—endocardial fibroelastosis of left ventricle, cardiomegaly, hydrothorax, hepatosplenomegaly
Baby of D. S. F.	SB	Intrauterine asphyxia secondary to loops of cord around neck
Baby of M. G. M.	SB	Anencephalic monster
Baby of R. E. G. E.	24 hr.	Kernicterus, imperforate anus, cleft palate
Baby of M. Q. C.	SB	No anomalies, mother with Class A diabetes mellitus
Baby of C. O. C.	SB	No anomalies, hypertensive disorder of pregnancy

SB = Stillbirth.

limbs) belonged to the group of nonoral contraceptive users.

Comment

By the introduction of contraceptive drugs, a major breakthrough in the problem of human population control seems to have been achieved. A large sector of the female population is now dependent upon the "pill" as an effective means of birth control.

There are, however, controversies as to the "pill's" other effects. Janerich and associates[4, 5] have reported congenital limb reduction defects associated with maternal oral contraceptive exposure with a preponderance in male offspring. Nora and Nora[6, 7] have also reported various cases of fetal abnormalities (vertebral, anal, cardiac, tracheal, esophageal, renal and limbs in the offspring of contraceptive users also with a preponderance among male children. However, these reports associate fetal anomalies with the use of six steroids during early stages of gestation, contrary to our study in which oral contraceptives were used prior to conception. Although both groups agree in their conclusions, their studies have been retrospective to the present time and neither can be taken as conclusive.

Reports have also been made in the literature of masculinization of the female fetus with the use of progestins during the first trimester of fetal life as a test for pregnancy.[8, 9]

Other authors believe that since the great majority of pregnancies preceded by use of oral contraceptives do not result in a defective offspring, some maternal predisposition is probably necessary before malformations occur. Some experimental animals have been used to induce congenital malformation with high doses of estrogen/progestin. But, on the basis of the effect of dosage, it is possible that the use of higher doses of contraceptive drugs would produce a higher frequency of abnormalities, as has been found with other established chemical mutagens.[5, 10–15] The fact remains that such high doses of contraceptive drugs are not at all in use by any human population, and efforts have been made to minimize the applied dose of the steroids to the lowest and safest possible levels. As stated earlier, our experimental group at the University of Puerto Rico received a total daily steroid dose of 5.75 mg (estrogen/progestin) and ranged from one to 29 cycles prior to pregnancy.

Still other authors like Klinger and associates[16] and Yasuda and Miller[17] have found no evidence that prior use of oral contraceptives alters the risk of chromosomally abnormal offspring or can be a cause of "transposition of the great vessels" in man.[16, 17]

In a study carried out by Fuertes-de la Haba and colleagues,[1] cell culture for chromosome studies was conducted in the oral and nonoral groups. No significant difference was found between groups.

Conclusion

As shown by our data in this report there is no statistical evidence whatsoever that the use of contraceptive pills affects the birth weight or causes fetal abnormalities in the offspring. The percentage of abnormalities in both groups was almost the same. The difference in incidence did exist between socioeconomic groups and a particular sex group in the percentage of abnormalities in general, although a consistent difference was observed between oral and nonoral groups in these variables. This may indicate that the preponderance of abnormalities in male children could have been influenced by sex or socioeconomic differences and not

by the use of contraceptive drugs, since the incidence differed between sex and socioeconomic groups but was the same between the oral and nonoral groups.

No correlation could be established between either the abnormalities found in our study group and the mother's age at the time of delivery of these children or the position of the children in relation to their siblings.

Although the reports in the literature have not been conclusive and since further studies on the use of sex steroids during pregnancy have to be done, it is our opinion that the use of these steroids should be avoided during early stages of gestation or if there is any doubt as to the existence of a breakthrough pregnancy.

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The effect of chlorotrianisene as postpartum lactation suppression on blood coagulation factors

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Coagulation changes and increased risk of thromboembolic disease may occur in association with estrogen administration. The puerperium is also a high-risk period for thromboembolism, and estrogen administration at this time may increase this risk. Patients with congenital deficiency of antithrombin III have recurrent venous thromboembolic disease, suggesting that low levels of this factor may be associated with "hypercoagulability" states. We studied 50 postpartum patients who received chlorotrianisene (Tace) or placebo for lactation suppression in a prospective, double-blind, randomized fashion. Antithrombin III values were significantly lower on the third day post partum in the treated group compared to the placebo group ($p < 0.05$). In addition, our clinical data from a total of 99 patients support the previous evidence that estrogens delay rather than prevent breast engorgement. Thus, with questionable benefit and a possible increased thromboembolic risk, it would appear prudent to discontinue the practice of estrogen administration for lactation suppression. (AM. J. OBSTET. GYNECOL. 134:518, 1979.)

VARIOUS estrogenic drugs have been used routinely for the suppression of postpartum lactation, to prevent the pain, discomfort, and milk leakage associated with excessive breast engorgement. Diethylstilbestrol (50 mg orally over 9 days, tapered dosage) and chlorotrianisene (Tace, 72 mg every 12 hours for 2 days) have been shown to suppress lactation compared to placebo during the immediate postpartum period.[1] However, these estrogens are no more effective than placebo if one- to four-week postpartum evaluations are done, as many patients have rebound engorgement.[1] Thus estrogens may delay rather than prevent postpartum lactation.

In addition, coagulation changes and increased risk of thromboembolic disease may occur in association with estrogen administration. It is well known that changes in blood coagulation factors occur during pregnancy. Several clotting factors increase in pregnancy: Factor VII and Factor X (Owren's P&P test), antihemophiliac factor (Factor VIII), fibrinogen, plasminogen, and antiplasmin.[2] There is also a decrease in fibrinolysis during pregnancy.[2] so that pregnancy has been considered a hypercoagulable state.

Three large retrospective studies[3–5] have shown that the incidence of puerperal thromboembolism was higher in women who received estrogen for lactation suppression compared with those who did not. In one study,[3] there was a tenfold increase in thromboembolism in low-parity women age 25 and older who were not lactating compared to those who were, and all eight cases of pulmonary embolism were in women who received estrogen for lactation suppression. In another

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**Hubert E. and Anne E. Rogers Scholar in Academic Medicine.*

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study,[4] inhibition of lactation by ethinylestradiol was associated with a threefold increase in thromboembolism. Other risk factors were age greater than 25, parity greater than three, or operative delivery. When inhibition of lactation is combined with any of these the risk of thromboembolism is further increased.[4, 5] Among women aged more than 35 years who have an operative delivery, inhibition of lactation with estrogen is accompanied by a tenfold increase in the incidence of puerperal thromboembolism.[4] Post partum, thromboembolic complications have been frequently associated with the use of oral contraceptives.[6]

Antithrombin III, otherwise known as heparin cofactor, is a naturally occurring inhibitor of Factor X. It is an alpha$_2$ globulin with a molecular weight of 60,000. Patients with congenital deficiency of this factor have recurrent venous thromboembolic disease.[7] and so a low level of this factor has been thought to be possibly associated with "hypercoagulability" states. Levels of antithrombin III have been shown to be decreased in women in the third trimester of pregnancy,[8-11] in women taking stilbestrol or quinestrol for lactation suppression,[8, 9, 11] in women taking estrogenic oral contraceptives,[10, 12, 13] and in postmenopausal women taking conjugated estrogens.[14]

Chlorotrianisene (Tace), a synthetic estrogen, has not been previously evaluated for its effect on coagulation factors. We studied hematologic and coagulation properties of blood in postpartum, nonlactating patients receiving chlorotrianisene compared with those receiving placebo.

Material and methods

All patients who had undergone vaginal delivery and who elected lactation suppression were candidates for the study. The study was approved by the Joint Committee on Clinical Investigation of the Johns Hopkins Hospital, and permission according to the Helsinki Declaration was obtained from each patient. Patients with a history of past thromboembolic disease, coagulation disorders, or who were receiving drugs of any kind on a regular basis were excluded from the study. Patients were assigned to receive chlorotrianisene or placebo according to a table of random numbers. Chlorotrianisene, 72 mg, or identical-appearing capsules containing corn oil as placebo were started within four hours post partum and were administered every 12 hours for four doses. Patients received no other drugs except for codeine and propoxyphene during the postpartum period. All patients had breast support and ice packs as needed.

Venous blood was sampled prior to administration of the first capsule and again on the third and eighth postpartum days. Determination of hematocrit, white blood cell count, and platelet count were performed by standard techniques.

Blood for coagulation studies was collected into 3.8% trisodium citrate (1:9V/V) in glass tubes. Plasma was prepared by centifugation of the whole blood for ten minutes at 1,100 g at 20° C. Prothrombin times were measured on fresh plasma, using an acetone-dried rabbit brain preparation (normal control, 16 seconds). The partial thromboplastin time was determined by the macrotechnique of Miale using Thromboflax Reagent (Ortho Diagnostics, Raritan, New Jersey) (normal control value 80 to 100 seconds). The plasma fibrinogen concentrations were measured by both the techniques of Clauss, and Ratnoff and Mensie. The normal range is 220 to 400 mg/dl of plasma. Antithrombin III values reported below were determined immunologically by the electrophoretic immunoassay of Laurell with modifications of the technique as described by Mammen.[15] The normal value for nonpregnant women is 200 + 20 μg/ml. Antithrombin III was also assayed for its biologic functional activity by the method of Gitel and Wessler.

Progesterone was measured by radioimmunoassay following the procedure of Abraham and associates and estradiol was measured similarly using an antiserum made against estradiol 17β-6-carboxymethyloxine-thyroglobulin.

The age, race, and parity of the patients were recorded as was the occurrence of temperature elevation. Patients were examined by one of three observers. Breast size was measured in centimeters with a tape measure from the midline to the anterior axillary line bilaterally. Congestion, secretion, and pain were recorded on a scale of 0 to 4. For purposes of analysis, mild or no engorgement or pain were combined (0, 1, 2 on the scale) and moderate or severe engorgement or pain (3 or 4 on the scale) were combined. Daily use of analgesics for breast pain was recorded, and one week post partum the patients were asked if they were satisfied with the study drug given.

Results

A total of 50 patients were studied and had blood drawn on the day of delivery and two days later; 26 received placebo and 24 received chlorotrianisene. The mean age in the treated group was 21 years and in the placebo group 20 years. Seventy-five percent of the treated and 85% of the placebo patients were black. Fifty-eight percent in both groups were nulliparous. Twelve of the treated group and 13 of the placebo group returned for evaluation on the eighth postpartum day.

Table I. Effect of chlorotrianisene on postpartum hematologic factors

Hematologic factors	*Tace and placebo*	*Day 1*	*Day 3*	*Day 8*
Hematocrit (%)	Chlorotrianisene	35.5 ± 0.7*	34.4 ± 1.0	38.2 ± 1.0*
	Placebo	33.3 ± 0.7	31.9 ± 0.9	34.9 ± 0.7
White blood count	Chlorotrianisene	14.9 ± 0.9	11.4 ± 0.8†	7.3 ± 0.6†
(x 10^3)	Placebo	15.1 ± 0.8	11.6 ± 0.5†	7.6 ± 0.5†
Platelet count	Chlorotrianisene	215 ± 10	226 ± 11*	312 ± 11*†
(x 10^3)	Placebo	247 ± 16	269 ± 11	370 ± 26†
Antithrombin III	Chlorotrianisene	201 ± 18	183 ± 14*	189 ± 13
(μg/ml)	Placebo	189 ± 11	224 ± 14	226 ± 13
Prothrombin time	Chlorotrianisene	100%	100%	100%
(% standard)	Placebo	100%	100%	100%
PTT	Chlorotrianisene	72.5 ± 2.1	73.4 ± 5.4	78.8 ± 3.4
(sec.)	Placebo	72.5 ± 3.5	69.5 ± 2.3	74.3 ± 3.4
Fibrinogen	Chlorotrianisene	350 ± 19	415 ± 30	362 ± 32
(mg%)	Placebo	368 ± 27	384 ± 21	344 ± 38

*$p < 0.05$ (t test) versus placebo of same day.
†$p < 0.05$ (t test) versus Day 1 of same group.

Table II. Clinical data (99 patients)

	Day 3		*Day 8*		*Day 3 or Day 8*	
Clinical data	*Chlorotrianisene (N = 53)*	*Placebo (N = 46)*	*Chlorotrianisene (N = 25)*	*Placebo (N = 21)*	*Chlorotrianisene (N = 53)*	*Placebo (N = 46)*
Fever 100.4° F	4%	4%	—	—	—	—
Breast engorgement moderate or severe	9%	11%	16%	5%	17%	13%
Percentage using analgesics for breast pain	8%	7%	8%	10%	9%	9%
Percentage of patients satisfied with drug	—	—	88%	90%	—	—

The laboratory values are recorded in Table I. On Days 1 and 8 the hematocrit was significantly higher in the treated group, but the mean values for both groups were in the normal range. The platelet counts were not statistically different on the day of delivery, but were significantly lower in the treated group on the third and eighth postpartum days, also all in the normal range.

There was no significant difference in the values for antithrombin III on the day of delivery. On Day 3 the concentration decreased in the chlorotrianisene group and increased in the placebo group for a statistically significant difference ($p < 0.05$). On Day 8 the trend remained but the concentration difference was not significantly different. The differences were thus due to failure of the treated group to develop postpartum elevations of the platelet count and antithrombin III values as were observed in the placebo group. The levels of antithrombin III were the same with both techniques employed.

There was no difference between the placebo and treated groups on Days 1, 3, and 8 for the following tests: white blood cell count, prothrombin time, partial thromboplastin time, fibrinogen (results were the same with both techniques employed), estradiol, and progesterone. Estradiol and progesterone concentrations decreased dramatically with time post partum as shown in Fig. 1, without differences between the treated and control groups.

An additional 49 patients were evaluated clinically but did not have blood drawn. Table II summarizes the clinical aspects of the total 99 patients. Fifty-three received chlorotrianisene, and 46 received placebo; 25 treated patients and 21 placebo patients returned for evaluation on the eighth postpartum day.

The incidence of fever of 100.4° F or greater on the third postpartum day was 4% in each group, and 9% versus 11% in the treated and placebo groups, respectively, had moderate or severe breast engorgement at that time. On the eighth postpartum day, only 5% of placebo-treated patients had moderate or severe breast engorgement compared to 16% of the chlorotrianisene-treated patients. Including moderate or severe breast engorgement occurring at any time post partum, 17% of treated patients and 13% of placebo patients were affected. There was no significant difference among any of these groups by chi-square analysis. Eighty-eight percent of treated patients and 90% of

placebo patients stated that they were satisfied with the medication given. The utilization of mild analgesics for breast pain during the postpartum period was 8% in the chlorotrianisene group and 7% in the placebo group. There was no clinical evidence of thrombophlebitis in any patient.

Comment

Evidence is accumulating that estrogen administration carries a risk of thromboembolic disease. We observed a statistically significant decrease in antithrombin III levels on the third postpartum day in patients who received chlorotrianisene, 72 mg every 12 hours for the first two days post partum, compared to those who received placebo. This finding is consistent with previous reports of decreased antithrombin III in women receiving diethylstilbestrol post partum,[8, 9, 11] in women on oral contraceptives,[10, 12, 13] and in postmenopausal women receiving estrogens.[14]

Following parturition there was a rapid fall in plasma progesterone and estradiol which was independent of chlorotrianisene treatment. Coincident with this rapid decrease in steroid hormones was a rise in antithrombin III in untreated women, and chlorotrianisene administration prevented the rise in antithrombin III in the treated patients. Platelets also rose post partum in the placebo group. Chlorotrianisene administration did not prevent the rise in platelet count, but on Days 3 and 8 the levels were significantly less than in the placebo group, a change not previously related to estrogen therapy. Although the differences are statistically significant, the values remain in the normal range and may not be of biologic significance. The fall in white blood cell count post partum was not influenced by chlorotrianisene administration.

The lower values for antithrombin III in the treated group are not as low as those reported for families with reported increase in thromboembolic disease,[7] as in these families the antithrombin III levels are reduced to 40 to 50% of normal (90 to 100 μg/ml). The values found in this study remained in the normal range and again may not be of biologic significance.

In addition, our results add support to the previous reports questioning the efficacy of estrogen for postpartum lactation suppression,[1] as the overall incidence of breast engorgement was the same in both groups. Our study showed increased delayed breast engorgement in the treated group, suggesting that estrogens

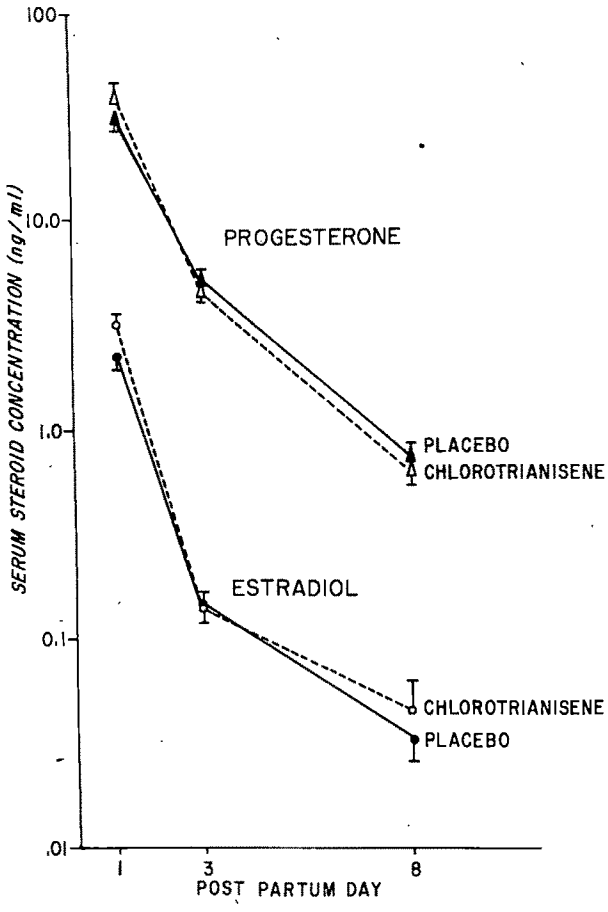


Fig. 1. Serum progesterone (△) and estradiol (○) decrease post partum and are not influenced by administration of chlorotrianisene.

postpone rather than prevent the engorgement. A recent study[16] showed increasing prolactin levels in women receiving stilbestrol post partum, compared to falling prolactin levels in patients receiving placebo. It thus appears that estrogen prevents the action of prolactin at the level of the breast, but when the estrogen is discontinued the prolactin levels are higher and probably contribute to rebound engorgement.

Thus with questionable benefit, if there is a possible thromboembolic risk with the use of estrogens, the risk-benefit ratio would clearly point to discontinuation of estrogen administration for this indication.

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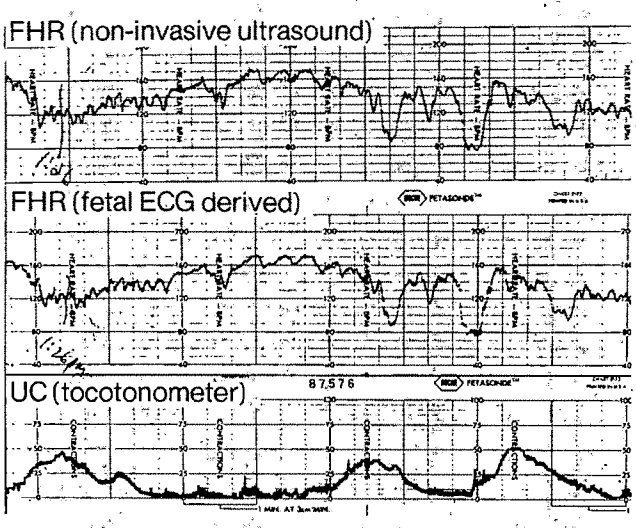
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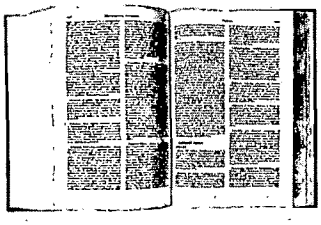
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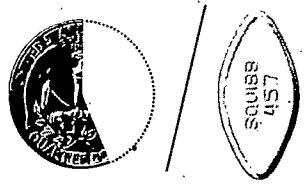
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Acceleration of the fetal heart rate during contractions was usually followed by deceleration, and evidence is presented to show that it results from increased sympathetic drive and may be associated with fetal tissue hypoxia. However, the presence of accelerations are not serious and merely warn the obstetrician of the possibility of the occurrence of subsequent decelerations. The mechanism thought most likely to produce accelerations is uterine compression of the umbilical vein during contractions. (AM. J. OBSTET. GYNECOL. 134:523, 1979.)

ACCELERATION of the fetal heart rate (FHR) during contractions is stated to be "not an adverse pattern," indicating good reflex responsiveness of the fetal circulation, the mean fetal pH in association with this change being normal (7.34 ± 0.03).[1] However, Paul[2] states that the clinical significance of acceleration during contractions is unclear, that the change is mediated through the sympathetic division of the autonomic resources system, and that it may be an early response to the stresses of labor. Accelerations may also occur before labor in the absence of contractions and these have been described by Schifrin[4] as a reactive pattern. Their appearance has been used as a positive indicator of good health of the fetus, over 700 fetuses with a reactive pattern having no serious problem in subsequent labor. The mechanism producing acceleration before and during labor may be different so that evidence of good health in one group may not be applicable to the other, but with the exception of Paul's[2] slight uncertainty, opinions favor the view that accelerations are not important clinically. We wish to present some data associated with accelerations in the human fetus and to discuss this in the light of other evidence, including study of the sheep fetus.

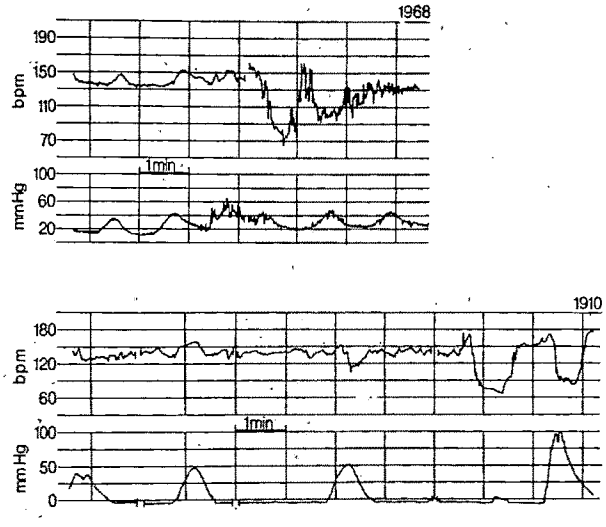


Fig. 1A. FHR uterine pressure recordings from two patients showing transition from transient accelerations or biphasic change to decelerations.

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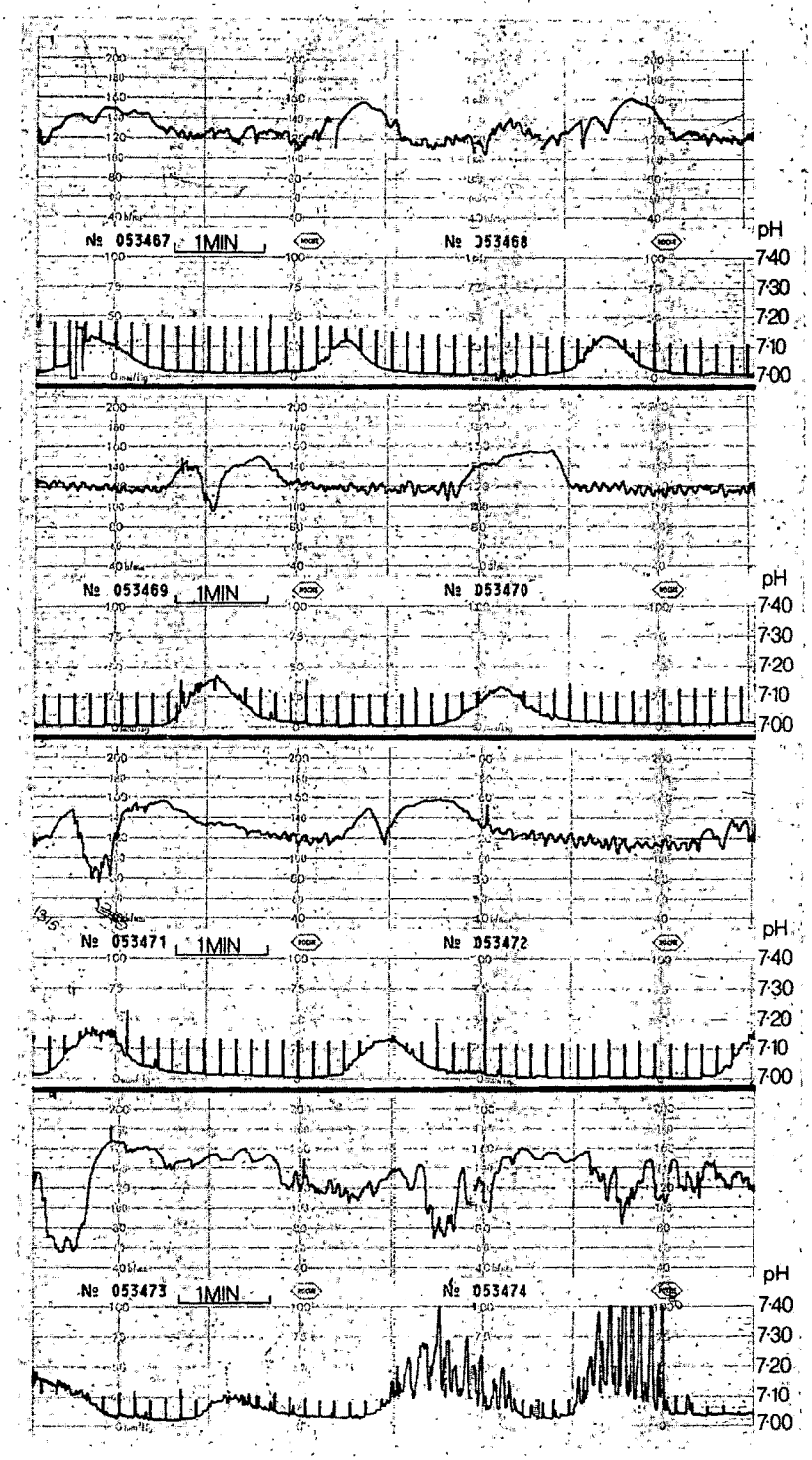


Fig. 1B. FHR, uterine pressure, and scalp tissue pH-(measured by the height of the vertical lines on the pressure trace) recording from patient showing transition from accelerations to biphasic change and decelerations. The scalp tissue pH has declined from 7.20 to 7.10 during the time of change in FHR pattern.

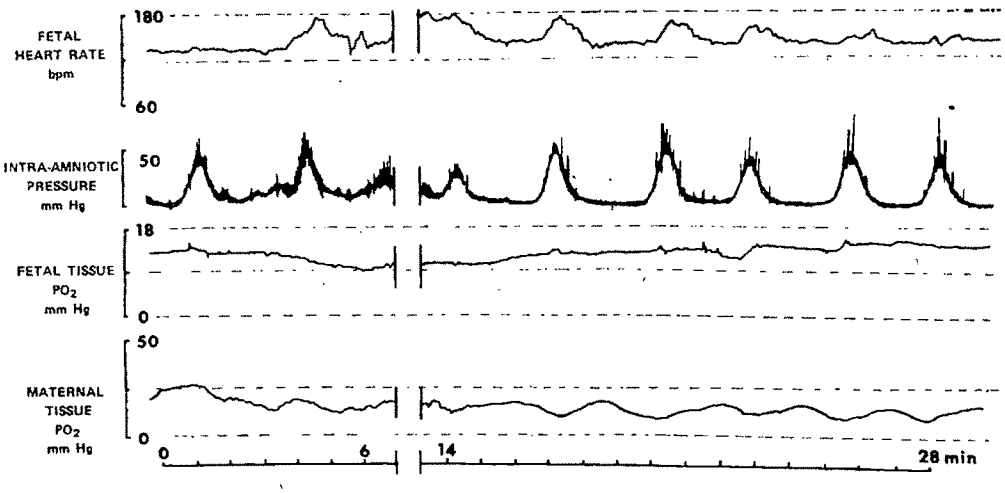


Fig. 2. Prolonged fall in fetal scalp Po_2 accompanied by marked rises in fetal heart rate with uterine contractions. As the magnitude of the accelerations diminshes, fetal tissue Po_2 returns to the basal level. (From Walker, A., Maddern, L., Day, E., Renou, P., Talbot, J., and Wood, C.: Fetal scalp tissue oxygen tension measurements in relation to maternal dermal oxygen tension and fetal heart rate, Br. J. Obstet. Gynaecol. **78**:1, 1979, published by Headley Bros.)

Material and methods

The records of 100 consecutive patients whose FHR was monitored by the fetal intensive care unit were examined for the appearance of accelerations. These were defined as an increase in FHR of more than 20 beats per minute in relation to a uterine contraction. All were patients whose fetuses were at increased risk because of the presence of obstetric complications such as hypertension, proteinuria, antepartum hemorrhage, fetal growth retardation, and low urinary estriol excretion. Patients received intramuscular Demerol, 100 to 150 mg, as an analgesic during the first stage of labor and nitrous oxide and oxygen mixtures during the second stage.

Results

FHR accelerations were present in 14 of the patients. In only three were accelerations not accompanied by other changes. The FHR traces of the remaining 11 patients showed both accelerations and decelerations. The accelerations always preceded the development of decelerations and in some instances the trace showed a gradual progression from accelerations, to acceleration and deceleration (biphasic change), to decelerations alone (Figs. 1A and 1B).

In the same 100 patients there were 11 with decelerations alone, nine beginning in the early-mid phase of the contraction cycle, and three in the late phase of the contraction cycle (one had both early-mid and late decelerations).

The occurrence of accelerations in association with decelerations was highly significant (Table I).

Overall comparison of two groups, accelerations + decelerations, and decelerations alone showed no difference in terms of age, parity, gestational length, length of labor, type of delivery, Apgar score, and fetal weight (Table II). The three patients with accelerations alone were not different from the remaining 11 of this group who had both accelerations and decelerations.

Comment

The reason for the association between accelerations and decelerations is very unlikely to be due to chance ($P < 0.001$) and the most likely explanation is that a single process causes both. As accelerations precede decelerations it is also likely that the acceleration represents an early stage of a physiologic or physiopathologic process which would support Paul's[2] view that it may be an early response to some stress.

Three pieces of evidence may throw light on the significance of the accelerations. Maternal injection of a beta-blocking drug abolished accelerations in relation to the contraction cycle in all of the eight fetuses.[3] This shows that the acceleration is proabably related to increased sympathetic drive. Studies of fetal tissue Po_2 show correlation between FHR accelerations and falls in fetal scalp tissue Po_2 (Figs. 2 and 3).[5] When the heart rate change is biphasic, the tissue Po_2 begins to fall at the time of the acceleration, suggesting that the acceleration represents an early stage of a hypoxic process.

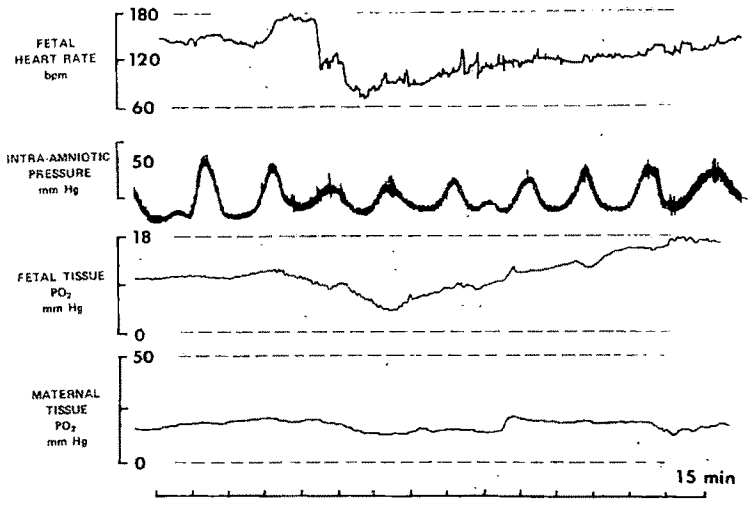


Fig. 3. Large fall in fetal scalp tissue Po_2 associated with a spontaneous biphasic change in fetal heart rate. The patient, who suffered from the supine hypotensive syndrome, was turned from the supine to the right lateral position at the 10 minute mark of this record. Note that the fall in tissue Po_2 began at the time of the acceleration and became more marked during the deceleration. (From Walker, A., Maddern, L., Day, E., Renou, P., Talbot, J., and Wood, C.: Fetal scalp tissue oxygen tension measurements in relation to maternal dermal oxygen tension and fetal heart rate, Br. J. Obstet. Gynaecol. **78**:1, 1979, published by Headley Bros.)

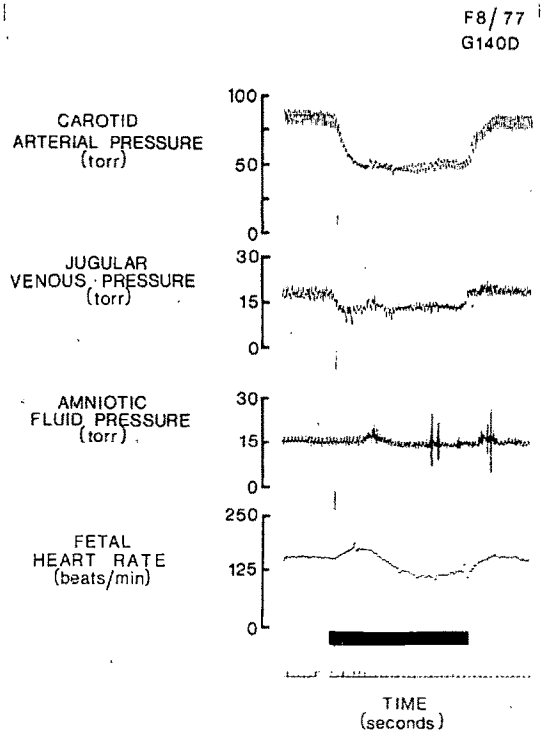


Fig. 4. Illustration of a bidirectional change in heart rate following brief inferior vena caval occlusion (bar) in a near term fetal lamb. Note that heart rate first increases (+20 beats/minute) then decreases (−45 beats/minute) from the baseline level in association with falls in both venous and arterial pressures. Caval occlusion was effected by inflating a balloon cuff which had been implanted around the vessel 30 days prior to the experiment.

Table I. Association between accelerations and decelerations

Accelerations	*Decelerations*	
	Yes	*No*
Yes	10	3
No	11	76

$\chi^2 = 28$; $p < 0.001$.

Table II

	Accelerations + decelerations	*Decelerations*
Age	21 ± 2.1	22 ± 2.5
Parity	1.7 ± 0.4	1.4 ± 0.3
Gestational length	283 ± 16	287 ± 13
Length of labor	8.1 ± 2.5	9.6 ± 3.4
Mode of delivery:		
Spontaneous	11	6
Forceps	2	4
Cesarean section	1	1
Fetal weight (gm)	3,310 ± 327	3,421 ± 285
Apgar score (1 minute)	7.2	7.2

Comparison of groups by χ^2 test and Student's t test showed no significant differences.

The final evidence concerns the biphasic change of FHR which occurs in the sheep fetus following brief inferior vena caval occlusion (Fig. 4). The fall of venous and arterial pressure occurs during both the acceleration and deceleration and could be expected to be as-

sociated with a reduction in cardiac output and, at least in some areas of the body, a fall of fetal tissue Po_2.

The hypothesis suggested from the observation and evidence cited is that accelerations are most likely a result of a reduction of venous return to the heart, perhaps from cord compression. The acceleration results from sympathetic stimulation as they are abolished by the action of a beta-blocking drug. The transient reduction in fetal scalp tissue Po_2 which occurs during accelerations cannot be assessed quantitatively, and judging from the case histories, in particular the fetal and neonatal status, the presence of accelerations have no clinical significance except to warn the obstetrician that decelerations may subsequently occur. The accelerations, however, are distinct from the transient increase of FHR, and reactive patterns described by Schifrin[4] which occur in the antepartum period in the absence of uterine contractions.

Other explanations of the data are possible and may involve any circulatory stress which initially would stimulate the sympathetic nervous system and then subsequently stimulate the parasympathetic system when the stress is more severe. However, none seems as likely to occur in utero as restriction of venous return resulting from uterine compression of veins, most likely the umbilical vein.

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Assessment of fetal lung maturity: A comparison of the lecithin/sphingomyelin ratio and the tests of optical density at 400 and 650 nm

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Seventy-eight amniotic fluid samples were obtained by transabdominal amniocentesis and were analyzed for their L/S ratio and optical density at 400 and 650 nm. The L/S ratio was considered to be mature if the values were greater than 2.0. The optical density of the fluids decreased with prolonged refrigeration. With freshly centrifuged samples, the OD_{650} reading of greater than 0.15 gave the best correlation with the mature L/S ratio. There were 3.8% false positive results and 14.1% false negative results. The study confirms that the OD_{650} test on fresh amniotic fluid is a rapid and inexpensive way to determine fetal maturity. All samples with values of less than 0.15 must, however, also be tested for their L/S ratio since some of the infants with these values may also be mature. (AM. J. OBSTET. GYNECOL. 134:528, 1979.)

A MAJOR PERINATAL MORBIDITY and mortality problem is the immaturity of neonates' lungs and their resultant respiratory distress. The introduction of amniotic fluid measurements of the lecithin to sphingomyelin (L/S) ratio by Gluck and associates[1] in 1971 provided obstetricians with an accurate means of assessing fetal lung maturation. The proper application of this test to women who are being considered for elective termination of pregnancy should eliminate the large number of iatrogenic cases of prematurity that occur.[2] When maternal and/or fetal diseases require early delivery, this test can give an accurate prediction of the neonatal risks of the intervention which is critical information for making the correct decisions. One problem with the new L/S test has been a technical one of getting accurate laboratory determinations at the smaller obstetric units. In order to overcome this problem simpler tests have been developed. Recently Sbarra and co-workers[3] have suggested that reading the optical density at 400 and 650 nm gave a good correlation with the L/S ratio. The purpose of this report is to compare the optical density test reading at both 400 and 650 nm with the classic amniotic fluid L/S ratio test. The results show that significant false negative errors can occur with the simple OD test and especially if the fluid is refrigerated for long periods before testing.

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Methods

Seventy-eight fresh amniotic fluid samples were selected for study. All of the fluids were obtained by transabdominal amniocentesis from women who were considered for delivery for medical reasons and where there was a question of fetal maturity. The medical reasons included hypertension, diabetes mellitus, Rh sensitization, intrauterine growth retardation, and previous cesarean sections. All of the patients signed an informed consent and all had ultrasound localization of the placenta and optimal amniocentesis site before the

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Table I. Frequency distribution of the amniotic fluid optical density at 400 nm in comparison to the L/S ratio (N = 77)

Test	*OD < 0.28 Immature*	*OD > 0.28 Mature*
L/S ratio <2.0 Immature	19 (24.7%)	17 (22.1%) False positive
L/S ratio >2.0 Mature	4 (5.2%) False negative	37 (48.1%)

Table II. Frequency distribution of the amniotic fluid optical density at 650 nm in comparison to the L/S ratio (N = 78)

Test	*OD < 0.15 Immature*	*OD > 0.15 Mature*
L/S ratio <2.0 Immature	34 (43.6%)	3 (3.8%) False positive
L/S ratio >2.0 Mature	11 (14.1%) False negative	30 (38.5%)

procedure. No fetal or maternal complications were encountered. The fluids which were highly pigmented or which contained blood or meconium were excluded since these substances are known to affect the L/S ratios.[4] The fluids were centrifuged within two to three hours of collection for 10 minutes at 3,000 rpm (2,500 × g) at 4° C in an International Model PR 600 centrifuge. The supernate was removed and divided into two aliquots. One aliquot of each sample was analyzed in duplicate for its L/S ratio by means of a modified thin-layer chromatographic technique.[5] The absorbance of the other aliquot was determined at wave lengths of 400 and 650 nm by means of a Beckman Model 25 DB recording spectrophotometer against distilled water within two hours of centrifugation.

Finally an experiment was performed to see the effects of prolonged refrigeration of amniotic fluids on the initial optical density. Four amniotic fluids were centrifuged as described and the optical density at 650 nm was read. The fluids were then placed in a refrigerator at 4° C and a repeat centrifugation and OD reading at 650 nm was done daily over a five-day period of time.

The paired sample results were analyzed with the aid of a computer and calculations were made of the correlation coefficients and the false negative and positive rates for the OD using an L/S ratio of 2.0 and above as indicating fetal lung maturity. Probability values were taken from two-tailed tables and only values of less than 0.05 were considered significant.

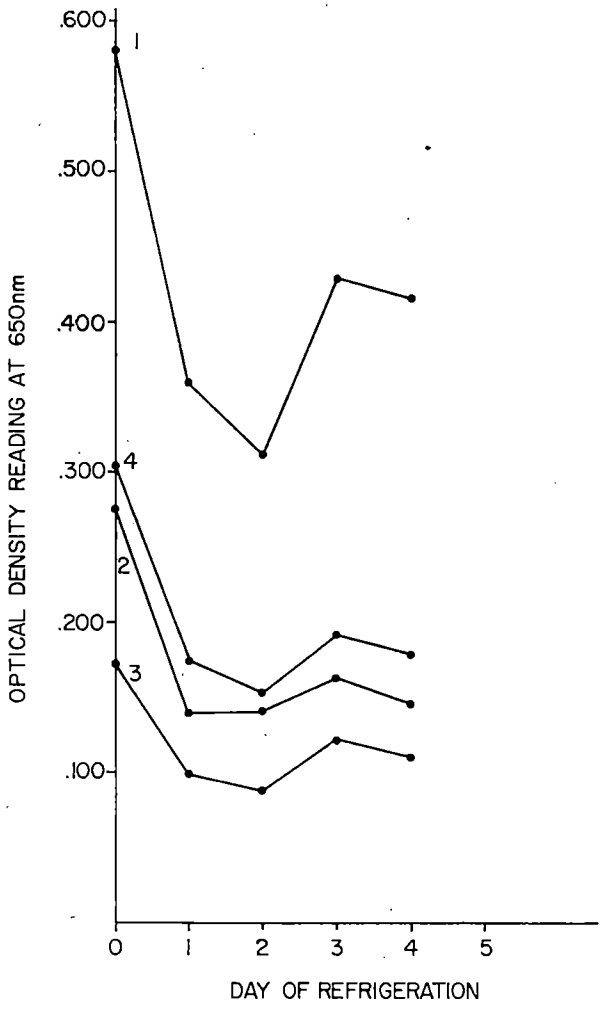


Fig. 1. The effect of prolonged refrigeration of amniotic fluids on the optical density reading at 650 nm (N = 4).

Results

A comparison of the L/S ratio and the OD at 400 nm and 650 nm results is seen in Tables I and II. Since Sbarra and colleagues[3] have used the OD reading of 0.15 or greater at 650 nm as an index of fetal maturity, this same value was studied here. The results show that the 650 nm values give an excellent prediction of the L/S ratio. The correlation coefficient for the L/S ratio and OD_{400} was 0.55 and for the OD_{650} it was 0.49 and both were statistically significant ($p < 0.05$). It can be seen that the false negative rate is 14.1% and the false positive rate is 3.8% for the 650 nm reading at 0.15.

When the OD reading at 0.28 or greater at 400 nm was used as an index of fetal maturity, the false positive rate was 22.1% and the false negative rate was 5.2%. When the OD_{400} reading of 0.35 or more was used, the false positive rate was 9.1% and the false negative rate was 14.3%.

The effects of prolonged refrigeration of amniotic fluids are seen in Fig. 1. It is clear that the optical density falls during the first two days and this is probably due to flocculation of the fluid proteins. This fall could bring a "mature" fluid to an "immature" reading at both wave lengths.

Comment

The need for a simple, rapid, reliable, and reproducible test of fetal lung maturity is well known to perinatologists. It has been established that the L/S ratio test does give an accurate prediction for most obstetric patients with the exception of those infants of mothers with diabetes mellitus.[5, 6] The L/S ratio test is somewhat complicated to perform, however, and it takes several hours to obtain the results. As a consequence some smaller obstetric services do not have the test available. Other simpler tests of fetal lung maturation have been developed and the one most widely tested has been the "shake" or "bubble" or "foam stability" test. Critical studies comparing that test with the L/S ratio show that the results can be quickly determined but there is a high false positive and false negative rate of interpretation.[7]

In 1976 Sbarra and co-workers[3] reported that the simple measurement of amniotic fluid optical density gave a good index of the L/S ratio. They originally suggested an OD of 0.28 or higher at 400 nm indicated fetal lung maturity with one false negative and no false positive results.[3] Because pigments such as bilirubin, meconium, and hemolyzed blood interfered at that wave length, they did their subsequent investigations at 650 nm.[3, 8-9] In an expanded study of 100 amniotic fluids they showed that the OD_{650} reading of 0.15 or higher gave a false negative rate for predicting a mature L/S ratio of 6% while the false positive rate was zero.[8] A later study of 300 amniotic fluids showed a 98% accuracy for prediction of the L/S ratio over two by measuring an OD at 650 nm of more than 0.15.[9] This method was also studied by Copeland and associates[10] on 87 amniotic fluids and they were less enthusiastic for although there were no false positive values, the false negative rate was 41%. A similarly disappointing set of results was found by Moodley and colleagues[11] on 127 fluids. They found a false negative rate of 32% and a false positive rate of 3% in attempting to predict a mature L/S ratio by the OD reading at 650 nm.[11] The results were better at 400 nm OD reading with a false positive rate of 6% and a false negative rate of 17%.[11]

Finally, Arias and co-workers[12] determined the OD_{400} (reading at 0.3), OD_{650} (reading at 0.15), and L/S ratio on 102 amniotic fluid samples. They noted a false positive rate of 18.1 and 11.0% and a false negative rate of 23.5 and 34.6% for the OD_{400} and OD_{650}, respectively.[12] Their conclusions were that the errors of the OD were too great to make the procedure at all applicable for perinatal assessments.[12]

Their high false negative rates might have been due to prolonged refrigeration of the fluids for it was shown in this study that that lowers the optical density. In addition, earlier studies have shown that the speed of centrifugation will affect the L/S ratio as low speeds give higher ratios than faster speeds. In this study it was noted that high centrifugation speeds gave lower absorbance. Therefore different investigators might get different results simply because of their speed of centrifugation.

The present study extends those observations and shows that prolonged refrigeration can lower the OD results. Also comparing the two OD readings the 650 nm gave the better results. With the OD_{650} reading of 0.15 the false positive rate for predicting a mature L/S ratio remains low (3.8%); however the false negative rate is still disturbingly high (14.1%). These figures suggest that the OD test cannot be the sole perinatal fetal maturation test but it can be used as a preliminary screening procedure. If a fetus is retained in utero during a high-risk pregnancy when it is really mature it could be damaged or die. This could happen in the 14.1% of the cases where the result is a false negative. Therefore, in order to avoid this problem all fluids with a negative OD_{650} reading must be further checked with an L/S ratio. The OD_{650} test is inexpensive and rapid and the information derived is valuable if the results are positive. When critical decisions such as referral to a tertiary care unit or premature delivery are to be made, it seems that the most sophisticated fetal maturity test possible must be available. As more studies are done, it may turn out that tests which are even more complicated than the L/S ratio such as the phosphatidyl glycero and phosphatidyl inositol measurements are the ones we will need for backup rather than the simpler ones such as the optical density determinations.[13] Further studies in this area are underway.

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Antepartum fetal testing

I. The oxytocin challenge test

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Two hundred seventy-eight high-risk patients were managed by a comprehensive assessment of the anatomic, biochemical, and functional environment of the fetoplacental unit utilizing predetermined guidelines. Decisions to terminate pregnancy were reserved for patients who demonstrated a positive OCT. Perinatal outcome in patients with positive OCT's was significantly worse than in patients who did not have a positive OCT. Patients with suspicious OCT's frequently had positive OCT's and were more likely to bear growth-retarded infants, whereas negative OCT's in general were associated with a favorable outcome. Correlation of estriol excretion with the OCT and perinatal outcome was inconsistent. There were a total of four prenatal deaths, all of which were considered unpreventable. (AM. J. OBSTET. GYNECOL. 134:532, 1979.)

A COMPREHENSIVE approach to the antepartum assessment of the intrauterine environment consists of adequate evaluation of the anatomic, biochemical, and functional status of the fetoplacental unit. In this institution, anatomic assessment involves routine ultrasound cephalometry during early gestation.[1] Biochemical tests include 24 hour urinary estriol determinations,[2] and amniotic fluid analysis for both the L/S ratio[3] and spectrophotometric analysis in instances of Rh isoimmunization.[4] Functional evaluation involves electronic monitoring of the fetal heart rate (FHR) for periodic changes in response to oxytocin-induced uterine contractions, the oxytocin challenge test,[5] and for accelerations in response to fetal movements,[6] a "nonstress" test.

With this information provided the task would be primarily to determine whether the intrauterine environment has been sufficiently compromised to warrant termination of the pregnancy, and then to select the appropriate time for intervention.

The present study was undertaken in order to evaluate the role of the functional methods of assessing the pregnancy at risk for fetal compromise and will be reported in two parts: Part I describes the experience and pregnancy outcome in patients who have undergone an oxytocin challenge test (OCT) and Part II describes the experience with a standardized nonstress test (NST).

Material and methods

During the interval between January, 1974, and July, 1977, a total of 420 OCT's were performed on 278 patients who were considered at risk for a compromised fetoplacental unit.

Patients selected for this test were admitted to the labor and delivery ward and were positioned at a comfortable recumbancy (approximately 30 to 40 degrees) with a slight left tilt. A continuous recording of the fetal heart rate (FHR) and uterine activity was accomplished by means of a Roche Fetal Monitor, Model Number 2102 or 2104. Maternal vital signs, including blood pressure, pulse, and temperature, were recorded at the outset and the blood pressure at periodic intervals for the duration of the test.

Oxytocin was administered with a Harvard constant-rate infusion pump, and the rate was increased at 15 minute intervals until uterine contractions occurred

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approximately every three minutes. The oxytocin infusion was discontinued when a recorded segment of one-half hour was available for analysis. Patients were subsequently observed while still being monitored until uterine activity subsided, and thereafter the test was terminated.

Tests were interpreted as being positive, negative, suspicious, hyperstimulation, or inadequate as follows: (1) positive: repetitive late decelerations with most uterine contractions; (2) negative: no FHR abnormalities with apparently adequate uterine contractions; (3) suspicious: occasional late decelerations; (4) hyperstimulation: FHR deceleration in response to a prolonged uterine contraction, or late decelerations occurring with uterine contractions observed at intervals of two minutes or less, and (5) inadequate: technical difficulties or instances in which the uterus was unresponsive to oxytocin.

Whenever possible, patients scheduled for an OCT underwent a 24 hour urinary estriol determination on a sample collected the day prior to the test.

In most patients the OCT was repeated at weekly intervals. In some instances, however, such as diabetes mellitus, severe hypertension, Rh sensitization, low or falling estriol levels, and suspicious OCT's, or when the intrauterine environment was considered unusually precarious, the test was repeated at more frequent intervals.

Management was determined on the basis of the results of the OCT in conjunction with other laboratory tests and the overall clinical picture. Patients who showed a negative OCT with normal estriols had repeat testing at weekly intervals, and with low or falling estriols were tested more frequently. Patients who demonstrated a positive OCT underwent an L/S ratio determination. If the L/S ratio was mature, delivery was planned either by oxytocin induction of labor when the cervix was favorable, or by cesarean section when the cervix was unfavorable or when the oxytocin induction was judged to be unduly hazardous to the fetus. If in the ensuing induction following a positive OCT late decelerations were not observed, the procedure was discontinued and the test considered false positive. If, however, late decelerations persisted in the ensuing induction, a presumption of a diminished fetal metabolic reserve was entertained, oxytocin discontinued, and a cesarean section undertaken. If the L/S ratio was immature, betamethasone induction of pulmonary surfactant, according to the protocol described by Liggins and Howie,[7] was instituted and delivery was planned 48 hours after the initiation of therapy. In the interim, patients were continuously monitored.

Patients who demonstrated a suspicious test were retested more frequently, and further management determined according to results of the repeated tests. Patients who showed a hyperstimulation or inadequate test were retested at a convenient time in the ensuing days. In spite of the adoption of these seemingly all-inclusive guidelines, it was necessary on occasion to modify the management based on the clinical condition of the individual patient.

Newborn infants were admitted to the neonatal division of the Perinatal Center, and underwent a complete physical and neurologic examination at an appropriate time after birth. Disturbances in growth characteristics were classified into: intrauterine growth retardation (IUGR) and large for gestational age (LGA), based on the criteria set forth by Usher and McLean,[8] and dysmaturity as described by Clifford.[9]

Table I. Number of patients and OCT's distributed according to groups* and type of test

	Group I	*Group II*	*Group III*	*Total*
No. of patients	35	93	150	278
No. of tests	77	146	202	425
Positive	37	0	0	37
Negative	26	127	179	332
Suspicious	10	7	9	26
Hyperstimulation	0	5	4	9
Inadequate	4	7	10	21

*For description of groups see text.

Table II. Distribution of patients with positive OCT according to management and outcome

No. of Patients	*Management–outcome*	*Comments*
11	Prompt cesarean section	2—High-risk fetus 9—Unfavorable cervix
2	No intervention— Fetal death in utero	1—Maternal viral pneumonia 1—Fetal anomaly
5*	Induction— No fetal distress*	3—Vaginal delivery 2—Cesarean section for cephalopelvic disproportion
17	Induction— Persistent fetal distress	15—Cesarean section 2—Vaginal delivery

*False positive 5/22 = 22.7%.

Results

The total number of patients were divided into three groups: Group I consisted of 35 patients who demonstrated at least one positive OCT; Group II consisted of 93 patients who had no positive OCT's, and whose pregnancies were complicated by diabetes mellitus, severe hypertension, severe pre-eclampsia, or low or falling estriols, in addition to those pregnancies which resulted in the birth of a neonate with IUGR, LGA, or

Table III. Comparison of outcome between patients with positive OCT and no positive OCT

	Positive OCT (Number = 21)		*No positive OCT (Number = 243)*		
	No.	*%*	*No.*	*%*	*p**
Cesarean section	19	90.5	41	16.9	<0.001
Meconium	9	42.9	51	21.1	<0.05
Estriol: low and falling	8	38.1	36	15.1	<0.01
IUGR	6	28.6	17	7.0	<0.001
Dysmaturity	6	28.6	36	14.9	NS
LGA	1	4.8	13	5.4	NS
Apgar: 1 min. ≤ 6	8	38.1	30	12.4	<0.01
5 min. ≤ 6	4	19.0	8	3.3	<0.001

*p in this and subsequent analyses, unless otherwise stated, means chi square test.

Table IV. Comparison of outcome between patients with positive OCT and patients with no positive OCT and high-risk factor

	Positive OCT (n = 21)		*No positive OCT and high-risk-factor (N = 92)*		
	No.	*%*	*No.*	*%*	*p*
Cesarean section	19	90.5	25	27.2	<0.001
Meconium	9	42.9	28	30.4	NS
Estriol: low and falling	8	38.1	36	41.0	NS
IUGR	6	28.6	17	18.5	NS
Dysmaturity	6	28.6	36	39.1	NS
LGA	1	4.8	13	14.1	NS
Apgar: 1 min. ≤ 6	8	38.1	15	16.3	<0.05
5 min. ≤ 6	4	19.0	4	4.3	<0.02

dysmaturity; Group III consisted of the remaining 150 patients who did not show positive OCT's and whose pregnancies and neonatal characteristics did not include those factors mentioned in Group II. Table I shows the number of OCT's and the distribution of the types of tests in each of the three groups described.

Table II summarizes the course of action and outcome in the 35 patients demonstrating at least one positive OCT. Eleven patients underwent cesarean section shortly after a positive OCT without an attempt at oxytocin induction, in nine of these patients because of an unfavorable cervix and in two patients because of multiple suspicious and positive OCT's. In two patients no action was taken and both resulted in fetal deaths seven and ten days, respectively, following the most recent positive OCT. The former patient had viral pneumonia with a tracheostomy and an unstable pulmonary status; at delivery there was a true knot of the umbilical cord. The latter patient had diabetes mellitus, with markedly immature L/S ratios, elevated amniotic fluid alpha fetoprotein levels, and radiologic evidence of fetal malformation; at delivery the stillborn infant was grossly deformed. Five patients underwent oxytocin induction following a positive OCT and no late decelerations were observed in the ensuing induction (false positive); three delivered vaginally after uncomplicated labor, and two delivered by cesarean section for cephalopelvic disproportion. Seventeen patients underwent oxytocin induction following their positive OCT's, and all patients demonstrated persistent late decelerations in the ensuing induction; 15 were delivered by cesarean section and two were delivered vaginally. The two latter patients were delivered of newborn infants who were clinically depressed at birth and both demonstrated scalp pH's of less than 7.15 shortly before delivery; the failure to expedite delivery was considered to be an error in judgment. In subsequent analyses, the group designated as positive OCT will exclude the five patients with false positive OCT's and the nine patients who underwent a prompt cesarean section for an unfavorable cervix since any of the latter could have had false positive OCT's. Of the 35 patients who had positive OCT's, four (11.4%) patients exhibited late decelerations with spontaneous uterine activity and therefore qualify as having had positive contraction stress tests; oxytocin was administered and all four patients continued to show late decelerations. Two were delivered by cesarean section and the remaining two patients (described above) were delivered vaginally.

Table III compares the outcome of patients with positive OCT's and patients who did not show positive OCT's. With the exception of neonates who were LGA and dysmature, all other factors occurred with more frequency in the positive OCT group. Table IV compares the outcome between patients with positive OCT's and patients with no positive OCT's and high-risk factors (Group II). Only the incidences of cesarean section and low Apgar scores were more frequent in the positive OCT group.

Table V compares the outcome in patients with positive OCT's and abnormal estriols to patients with positive OCT's and normal estriols. No significant differences were observed in the characteristics evaluated.

Suspicious OCT's were observed in seven patients with positive OCT's (7/35 = 33.3%), compared to 15 patients in combined Groups II and III (15/243 = 6.2%), and this difference was significant ($p = < .001$). Moreover when patients with suspicious OCT's were collectively compared with the remaining population of patients, both infants with IUGR and those with one-

minute Apgar scores ≤6 were significantly more frequent in patients with suspicious OCT's.

Analysis of the time interval between a negative OCT and either a positive OCT or late decelerations in labor was undertaken. In Group I, of the 21 patients with positive OCT's, two were followed by fetal death, and four patients had only one OCT which was positive. Of the remaining 15 patients, there were eight patients in whom a negative OCT was followed by a positive OCT within three days, two patients within seven days, and five patients more than seven days. One patient had a negative OCT interposed between two positive OCT's that were undertaken three days apart. In Group II there were 73 patients and in Group III there were 117 patients in whom the most recent negative OCT was undertaken within one week of delivery and there were no fetal deaths in either group. In Group II, however, five of the 73 patients (6.8%) showed late decelerations in labor; in one patient immediately after completion of the negative OCT, in two patients one day after the negative OCT, and in two patients four days after the negative OCT. In Group III two of the 117 patients showed late decelerations in labor (1.7%) and in both instances the oxytocin induction was undertaken immediately after completion of the negative OCT.

There were 26 infants with IUGR who had both OCT's and estriol determinations; 10 (38.5%) had positive OCT's, 15 (57.7%) had low or falling estriols, and 8 had neither of the two abnormalities.

Table VI describes the frequency of spontaneous rupture of the membranes and the occurrence of spontaneous labor within 24 hours of OCT's undertaken before 38 weeks and at 38 weeks' gestation or more. In the preterm interval there were two patients who developed spontaneous labor within 24 hours of the OCT at 36 weeks and 37 weeks, respectively, and the outcome in both infants was uncomplicated.

There were four perinatal deaths in the population studies: two fetal deaths in utero described earlier, and two neonatal deaths because of severe congenital malformations incompatible with life. The perinatal mortality rate corrected for severe malformations was, therefore, 3.6 per 1,000 live births.

Comment

The development of the OCT as a method of assessing the functional environment of the fetus without imposing a threat to its existence has undoubtedly been a breakthrough in modern obstetric practice. In the present study, aside from two patients who developed spontaneous premature labor within 24 hours of the test, no maternal or fetal complications could be directly attributed to the procedure.

Table V. Comparison of outcome between patients with positive OCT and normal estriol and patients with positive OCT and abnormal estriol

	Positive OCT normal estriol (N = 13)*		*Positive OCT abnormal estriol (N = 8)*	
	No.	*%*	*No.*	*%*
Cesarean section	11	84.6	8	100.0
Meconium	5	38.5	4	50.0
IUGR	3	23.1	3	37.5
Dysmaturity	4	30.8	2	25.0
LGA	0	0.0	1	12.5
Apgar: 1 min. ≤ 6	4	30.8	4	50.0
5 min. ≤ 6	2	15.4	2	25.0

*Fischer's exact test for comparison of the proportions in the two groups was not significant.

Table VI. The occurrence of spontaneous rupture of the membranes and spontaneous labor within 24 hours of the OCT

	No.	*Spontaneous labor*	*Spontaneous rupture of membranes*
<38 wk.	158	2(1.3%)	0
≥38 wk.	267	15(5.6%)	7(2.6%)
Total	425	17(4.0%)	7(1.6%)

There were four perinatal deaths and all were considered unpreventable. In one patient with fetal death in utero, no intervention was undertaken because of the critical condition of the mother, and in the remaining three patients fetal and neonatal deaths occurred because of severe malformations. Adherence to the guidelines adopted at the outset of the study is felt to be responsible for this favorable outcome.

The occurrence of late decelerations in response to either spontaneous or oxytocin-induced uterine contractions has been shown to be associated with fetal acidosis,[10] low Apgar scores, and a significantly large percentage of infants with poor outcome.[11] Persistent late decelerations following a positive OCT in all likelihood, therefore, should serve as a valuable indicator of a diminished fetal metabolic reserve and a cesarean section in these instances would be justified as a therapeutic measure to prevent fetal deterioration. Early intervention in these patients may explain the relatively high number of newborn infants with good Apgar scores in spite of persistent late decelerations following their positive OCT. The results of the present study corroborate these observations: in the only two patients in whom delivery was not expedited following a posi-

tive OCT, fetal death occurred shortly thereafter, and in the two patients who continued to show late decelerations in the ensuing induction following a positive OCT, and in whom a cesarean section was not undertaken, resulted in the birth of depressed infants. In addition, high-risk factors such as meconium staining of the amniotic fluid, low or falling estriol levels, IUGR, and low Apgar scores were more frequent in patients with positive OCT's when compared with patients who did not have a positive OCT, and as would be expected, cesarean sections were also undertaken with more frequency in those patients. However, when patients with positive OCT's were compared with patients in Group II who did not have a positive OCT but whose pregnancies were at risk for a compromised metabolic reserve, the only difference observed was lower one- and five-minute Apgar scores and again, as would be expected, a high cesarean section rate. Modanlou and colleagues[12] have shown that a low one-minute Apgar score reflects low fetal scalp pH's and a low five-minute Apgar score reflects on an even more profound depression of fetal scalp pH's. The results of the present study further confirm that even when factors such as meconium, abnormal estriol excretion patterns, and IUGR were equally distributed among a high-risk population of patients, those with positive OCT's were metabolically more compromised and, therefore, more likely to be delivered by cesarean section.

The implication of a false positive OCT is that even though repetitive late decelerations were observed for the duration of the test, the metabolic condition of the fetus is in reality undisturbed. The most plausible explanations have been set forth by Freeman and associates[13] who attribute the phenomenon, among other causes, to the transitory compression of the inferior vena cava while patients are in the recumbent posture. In the present study roughly 23% of patients with positive OCT's had a false positive test. From the standpoint of clinical management, therefore, it would be desirable to consider all patients with positive OCT's collectively as being at risk and institute the appropriate therapeutic guidelines adopted at the outset. If in so doing it becomes apparent that the test was false positive, subsequent management should then be modified to suit the individual patient.

The negative OCT in general was associated with a favorable outcome; however, there were many instances in which negative OCT's were observed in very close proximity to positive OCT's and a few instances in which late decelerations were observed during the ensuing labor following a negative OCT. Moreover, of the 26 growth-retarded infants born during this study, only ten had positive OCT's and the remaining 16 had negative OCT's. Although fetal death within one week of a negative OCT was not observed in the present study, and only very rarely in previous reports,[14, 15] the fact remains that fetal death is a somewhat inappropriate end point for the assessment of fetal health.

Suspicious OCT's were observed with more frequency in patients with positive OCT's than in patients with negative OCT's. In addition, patients with suspicious OCT's were more likely to bear growth-retarded infants. These observations justify more frequent evaluations of the functional environment of the fetus in patients who have demonstrated a suspicious OCT.

The results of this study have also shown that the correlation between abnormal estriol excretion and the results of the OCT and neonatal outcome was somewhat disappointing. Patients with positive OCT's were more likely to have abnormal estriols when compared with patients who did not have positive OCT's. However, of the 21 patients with positive OCT's only eight had abnormal estriols, and of the 26 growth-retarded infants only 15 had abnormal estriols. Moreover, the outcome in patients with abnormal estriols and positive OCT's was not significantly different when compared with the outcome in patients with normal estriols and a positive OCT, indicating that in patients with positive OCT's the finding of abnormal estriol does not necessarily signify a more seriously compromised fetus.

In conclusion, the results of this study have revealed a number of inconsistencies which place some limitations on the information that can be derived from the tests outlined. Both negative OCT's and normal estriols were certainly informative but did not invariably reflect a healthy fetal environment, whereas suspicious OCT's served as a warning for possible impending problems. A positive OCT, however, was invaluable in detecting the seriously compromised fetus and in determining the most opportune time for intervention. The latter conclusion should be weighed against the fact that of the 425 OCT's performed there were only 37 positive tests, a ratio which leaves much to be desired.

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Antepartum fetal testing

II. The acceleration/constant ratio: A nonstress test

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For a period of one-half hour of undisturbed fetal monitoring, periodic changes of the FHR in response to spontaneous fetal movements (FM's) were recorded. FM's in patients who subsequently had positive OCT's were less likely to show accelerations ($p = <0.001$) and more likely to show variable decelerations ($p = <0.001$) and no change ($p = <0.001$) in the FHR when compared with patients who did not have a positive OCT. A ratio between the number of FM's associated with accelerations and the sum of FM's associated with no change and decelerations was defined as the acceleration/constant (A/C) ratio. The outcome in patients who exhibited reactive tests (i.e., A/C ratio >1) was more favorable than the outcome in patients with nonreactive tests (i.e., A/C ratio ≤1). Patients with positive OCT's universally showed nonreactive tests, whereas patients with false positive OCT's were more likely to have reactive tests. Evidence is presented to suggest that the A/C ratio is more predictive of the intrauterine environment than the OCT. (AM. J. OBSTET. GYNECOL. 134:538, 1979.)

AT THE outset of electronic monitoring of the fetal heart rate (FHR), efforts were directed toward defining the pathophysiologic basis for periodic decelerations in response to uterine contractions and their relation to neonatal outcome.[1] Accelerations of the FHR were observed but their significance eluded definition until Lee and associates[2] reported that their occurrence was invariably associated with a favorable neonatal outcome. Since then several investigators have corroborated this observation.[3-6]

The finding that late decelerations were associated with fetal asphyxia and metabolic acidosis[7] led to the development of the oxytocin challenge test.[8] Along the same lines, the finding that FHR accelerations were associated with a good outcome resulted in the emergence of the "nonstress test" (NST). The term was chosen on the grounds that the desired end point, FHR accelerations, was not invoked by an external stressful stimulus.

Table I. Distribution of patients with positive OCT's according to management and outcome

No. of patients	*Management-outcome*	*Comments*
4	Prompt cesarean section	2–Unfavorable cervix
1	No intervention—fetal death in utero	Fetal anomaly
3*	Oxytocin induction—no fetal distress	1–Vaginal delivery 2–Cesarean section for cephalopelvic disproportion
7	Oxytocin induction—persistent fetal distress	7–Cesarean section

*False positive OCT 3/10 = 30%.

The standards, however, that have been employed both in the technique and definition of nonstress testing have varied. The present study describes a standardized NST based on the response of the FHR consequent to spontaneous and unprovoked fetal movements (FM's) within a finite period of time; the study also attempts to define the predictive value of this test

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Table II. Results of the non-stress test distributed among two groups*

	Group I	*Group II*	*p*†
No. of patients	10	142	
No. of tests	24	204	
No. of movements	13.38 ± 8.26	12.25 ± 4.98	NS
Accelerations	1.04 ± 1.43	5.10 ± 3.79	<0.001
No change	6.00 ± 4.35	3.26 ± 2.97	<0.001
Deceleration	2.13 ± 2.54	.41 ± .96	<0.001
Artifact	4.21 ± 4.48	3.47 ± 3.73	NS
No change + decelerations	8.13 ± 5.17	3.67 ± 3.24	<0.001

*For description of Groups see narrative.
†Two-tailed t test.

in identifying the fetus at risk, by comparing it with the oxytocin challenge test (OCT), estriol excretion, and neonatal outcome.

Materials and methods

Between January, 1976, and July, 1977, consecutive NST's and OCT's were performed on 157 patients who were considered at risk for a compromised fetoplacental unit. For a period of one-half hour of continuous FHR monitoring prior to an OCT, patients were instructed to signal an observer every time a FM was appreciated, and a mark was inserted at the appropriate point on the recording strip.

A periodic change of the FHR in response to each individual and unprovoked FM was clasified as either acceleration, no change, deceleration, or artifact according to the following: (1) acceleration: an acceleration of the FHR to a peak of 15 beats per minute (bpm) or more and lasting 10 seconds; (2) no change: no significant alteration in the constancy and beat-to-beat variability of the FHR; (3) deceleration: a variable type deceleration with a peak of 15 bpm or more and lasting 10 seconds; and (4) artifact: a noninterpretable segment of the FHR. A rapid succession of FM's occurring within a 20 second interval was scored as one movement. Moreover, if a prolonged acceleration was observed, the number of FM's occurring within the time span of the acceleration was collectively counted as one movement.

Immediately upon completion of the NST, an OCT was conducted. Management in each individual patient was undertaken on the basis of the results of the OCT in conjunction with other laboratory tests and the overall clinical picture as outlined in Part I of this study.

Results

The total number of patients who underwent consecutive fetal movement acceleration tests and OCT's was divided according to the outcome of the OCT into two groups: Group I consisted of 15 patients who had shown at least one positive OCT, and Group II consisted of the remaining 142 patients who had no positive OCT's.

The outcome of the 15 patients who demonstrated positive OCT's is shown in Table I. Four underwent prompt cesarean section without an attempt at oxytocin induction, two for an unfavorable cervix and two for an unusually precarious intrauterine environment as evidenced by multiple suspicious and positive OCT's. In one patient no action was taken because of elevated amniotic fluid alpha fetoproteins and radiologic evidence of fetal anomalies; fetal death in utero occurred ten days following the last positive OCT. Three patients underwent an oxytocin induction following the positive OCT and no late decelerations were observed in the ensuing induction (false positive). Seven patients underwent oxytocin inductions after a positive OCT and all were delivered by cesarean section because of persistent late decelerations in the ensuing induction. In subsequent analyses, the group designated as positive OCT will exclude the three patients who had false positive OCT's and the two patients who underwent prompt cesarean section for an unfavorable cervix since either of the latter two could have had a false positive OCT.

Table II shows the results of the NST in the two groups described. Statistical analysis, utilizing two-tailed tests, showed no significant differences in the number of movements, and the number of artifacts. Accelerations, however, were less frequent in Group I, and no change, decelerations, and the sum of no change and deceleration were more frequent in Group I.

Based on these observations, a ratio between the number of FM's that were associated with accelerations of the FHR divided by the sum of FM's associated with no change and those associated with decelerations was constructed. This was defined as the acceleration/ constant (A/C) ratio as follows:

Table III. Characteristics of patients with positive OCT's

Case No.	*Maternal diagnosis*	*Days before delivery*	*A/C ratio**	*OCT†*	*Estriol*	*Neonate*
I-16	Suspected post-datism	0	$\frac{0}{0+2}$	P	N	AGA‡
I-18	Rh disease	16	$\frac{5}{13+5}$	—		
		7	$\frac{0}{0+3}$	P		
		6	$\frac{0}{3+4}$	S		
		2	$\frac{0}{6+0}$	P	Low	AGA
I-20	Suspected post-datism	3	$\frac{0}{5+0}$	N		
		2	$\frac{0}{6+3}$	S		
		0	$\frac{0}{6+3}$	P	Low	IUGR
I-21	Diabetes mellitus	15	$\frac{0}{7+8}$	—		Congenital malformation
		11	$\frac{1}{5+9}$	N		
		10	$\frac{0}{13+5}$	P	Low	Stillborn
I-22	Pre-eclampsia mild	32	$\frac{1}{0+0}$	N		
		3	$\frac{2}{2+0}$	—		
		0	—	P	Low	IUGR
I-23	Diabetes mellitus	8	$\frac{3}{5+0}$	N		
		5	$\frac{2}{6+1}$	P		
		5	$\frac{0}{4+1}$	N		
			$\frac{1}{9+1}$	P	Low	LGA
I-26	Hypertension	10	$\frac{4}{18+0}$	S		
		3	$\frac{2}{7+1}$	N		
		3	—	P	N	AGA
I-29	Suspected IUGR	20	$\frac{0}{10+0}$	N		
		8	$\frac{2}{7+0}$	N		
		0	—	P	N	IUGR
I-32	Suspected IUGR	4	$\frac{2}{2+3}$	—		
		1	$\frac{0}{7+1}$	S		
		0	—	P	N	IUGR
I-33	Suspected IUGR	0	$\frac{0}{3+1}$	P	Low	IUGR

*A/C ratio = Accelerations/no change + decelerations.
†OCT (P = positive, S = suspicious, N = negative).
‡AGA = appropriate for gestational age.

Table IV. Comparison of outcome with the nonstress test and between patients with positive OCT and no positive OCT

	Positive OCT (N = 10)		*No positive OCT (N = 142)*		
	No.	*%*	*No.*	*%*	*p**
Cesarean section	10	100.0	25	17.6	<0.001
Meconium	5	50.0	30	21.1	<0.05
Estriol: low or falling†	6	60.0	20	15.4	<0.001
IUGR	5	50.0	12	8.6	<0.001
Dysmaturity	0	0.0	15	10.6	NS
LGA	2	20.0	4	2.8	<0.01
Apgar: 1 min. ≤ 6	4	40.0	14	9.9	<0.01
5 min. ≤ 6	2	20.0	3	2.1	<0.01
Number of NST's	24		204		
Nonreactive tests	23	95.8	71	34.8	<0.001
Tests with decelerations	15	62.5	45	22.1	<0.001
Tests with <3 accelerations	20	85.7	58	28.4	<0.001

*p in this and subsequent analyses means chi square test.

†Only 130 of 142 patients with no positive OCT had estriol determinations.

$$\text{A/C ratio} = \frac{\text{Accelerations}}{\text{No change + decelerations}}$$

An NST in which accelerations of the FHR in response to FM were preponderant would show an A/C ratio of more than one; this was defined as a reactive test. An NST in which the majority of FM's were associated with either no change or decelerations of the FHR would show an A/C ratio of less than one; this was defined as a nonreactive test. Of the total 237 tests performed, there were 12 in which the A/C ratio was exactly one: two in Group I (one associated with a positive OCT and one with a false positive OCT) and ten in Group II. A test with an A/C ratio of exactly one was defined as a nonreactive test.

Table III outlines the details of the NST's in relation to the OCT, time before delivery, estriol excretion, and outcome in the ten patients with positive OCT's.

Table IV compares patients with positive OCT's and patients who did not have a positive OCT with respect to the distribution of a number of maternal and neonatal characteristics and to the distribution and variables of the NST.

Next, the total population of patients was divided into two groups: 58 patients who had at least one nonreactive test within one week of delivery and 61 patients who had a reactive test within one week of delivery, and Table V compares outcome between these two groups.

Table VI shows the details of the NST's in relation to the OCT's, time before delivery, estriol excretion, and outcome in the three patients with false positive OCT's.

Table V. Comparison of outcome between patients with nonreactive and with reactive NST's undertaken within one week of delivery

	Nonreactive NST (N = 58)		*Reactive NST (N = 61)*		
	No.	*%*	*No.*	*%*	*p*
Cesarean section	22	37.9	9	14.8	<0.01
Meconium	11	19.0	14	22.9	NS
Estriol: low or falling*	19	33.3	8	15.1	<0.01
IUGR	11	19.0	3	4.9	<0.02
Dysmature	5	8.6	11	18.0	NS
LGA	6	10.3	5	8.2	NS
Apgar: 1 min. ≤ 6	10	17.2	4	6.6	NS
5 min. ≤ 6	1	1.7	0	0.0	NS
Number of NST's	79		63		
Positive OCT's	13	16.5	2	3.2	<0.01
Suspicious OCT's	8	10.1	2	3.1	NS
Tests with decelerations	31	38.3	4	6.2	<0.001
Tests with <3 accelerations	50	63.3	2	3.2	<0.001

*Only 57 of 58 patients with nonreactive NST's and 53 of 61 patients with reactive NST's had estriol determinations.

There were 16 suspicious OCT's with concomitant NST's of which 13 (81.3%) were nonreactive, 9 (56.3%) showing <3 accelerations, and 6 (37.5%) showing decelerations.

Finally, Table VII describes the frequency of positive OCT's, nonreactive NST's, and abnormalities in estriol excretion in neonates with a disturbance in growth during intrauterine development.

Comment

The results of this study have shown that periodic changes of the FHR consequent to spontaneous and unprovoked FM's show a good correlation with fetal outcome. FM's in patients with positive OCT's were rarely associated with accelerations and frequently associated with variable type decelerations or no change of the FHR. Conversely, FM's in patients who did not show positive OCT's were frequently associated with accelerations and rarely associated with decelerations of the FHR. These observations formed the basis for constructing the A/C ratio in an effort to provide for a quantitative method of assessing the degree of reactivity of the FHR within a finite period of time.

Analysis of the data based on the A/C ratio supported the ratio as a sensitive method for predicting neonatal outcome. Nine of ten patients and 23 of 24 NST's performed on patients with positive OCT's showed nonreactive ratios and the only one reactive

Table VI. Characteristics of patients with false positive OCT*

Case No.	Maternal diagnosis	Days before delivery	A/C ratio	OCT	Estriols	Neonate
I-19	Myomatous uterus	1	5/5 + 0	P	Low	AGA
I-25	Pre-eclampsia, mild	15	3/2 + 0	N		
		8	3/2 + 0	P		
		2	4/3 + 0	N	N	AGA
I-30	Suspected IUGR	2	8/2 + 0	P		
		1	7/8 + 0	N	N	AGA

*For abbreviations see legend in Table III.

Table VII. Antenatal characteristics of newborn infants with disturbances in growth during intrauterine development

	Dysmature (N = 24)		LGA (N = 7)		IUGR (N = 19)	
	No.	%	No.	%	No.	%
Positive OCT	2	8.3	1	14.3	6	31.5
Estriol, low or falling	3	12.5	2	28.6	9	47.3
Nonreactive NST	7	29.2	4	57.1	13	68.4
At least one abnormal test	8	33.3	4	57.1	17	89.4

test was observed 32 days before delivery of an infant with IUGR. In contrast, patients who did not show a positive OCT demonstrated a strikingly higher number of reactive ratios. Furthermore, the A/C ratio provides an additional dimension to the assessment of the reactivity of the FHR by incorporating into the final formula FM's associated with no change and decelerations, since the latter two were significantly more frequent in patients with positive OCT's.

Several observations seemed to suggest that the A/C ratio is more sensitive than the OCT as an indicator of fetal compromise: (1) the NST's that were performed on patients who later in the course of their antenatal testing demonstrated a positive OCT were almost universally nonreactive; (2) patients who had false positive OCT's were more likely to have reactive NST's; and (3) newborn infants with IUGR and LGA more often showed nonreactive NST's than positive OCT's.

The hypothesis of this study is predicated on the clinical observation that motion of a healthy fetus results in acceleration of the heart rate, whereas in the case of an unhealthy fetus motion seldom results in accelerations, and often results in decelerations or no change of the heart rate. The regulation of myocardial contractility is under control of the components of the autonomic nervous system, the sympathetic and parasympathetic, which exert contrasting effects upon the different tissues of the heart.[9] Adrenergic impulses in general increase the contractility of the atrial and ventricular muscles, whereas cholinergic impulses exert an opposing effect. Equipped with these two mechanisms, the organism is capable of maintaining a fine adjustment in cardiac rhythm in the face of a constantly changing environment. When the organism is challenged, the sympathetic system is called upon to discharge as a unit, thereby exerting an effect on all tissues innervated by that system including the myocardium, with the resultant increase in the heart rate and blood pressure.

Regulation of the heart rate of the fetus has been shown to be under control of the autonomic nervous system.[10] With a minor challenge such as motion, it is not clear whether acceleration of the heart rate is a result of a discharge of sympathetic activity or a release of parasympathetic inhibition, although evidence suggests that the sympathetic system predominates in the control of cardiac rhythm during fetal life.[10] It is possible that a fetus with diminished metabolic reserve exhibits a general lassitude of the autonomic nervous system and consequently fails to manifest accelerations of the heart rate with motion.[11] In addition, the existence of a weak circulatory system may be responsible for a loss of turgor of the umbilical cord; motion of the fetus in this instance would predispose the vulnerable cord to entanglement and therefore variable-type decelerations.

In the present study, the one-half hour segments considered for analysis were spontaneous and no effort was made to arouse the quiescent or "sleeping" fetus.

In the interest of exactitude, NST's should be conducted in a uniform manner where either all movements that are spontaneous should be considered for analysis or all fetus' should be challenged by a measurable and reproducible stimulus, be it sound,[12] light, or tactile arousal.

The term nonstress test (NST) was used in this study in order to comply with existing nomenclature, although in the opinion of the authors it is somewhat nonspecific. The term encompasses any number of tests in which a stressful challenge was not exerted in order to elicit the desired end point. The term fetal acceleration determination (FAD) test proposed by Lee and Associates[4] is more descriptive but still nonspecific since it can describe any test which determines accelerations of the FHR. The authors propose the term "fetal movement acceleration test" (FMAT) because it describes the two most salient features of this test, namely FM's as well as accelerations of the FHR. In addition, it provides a latitude of flexibility since it can be adjusted to accomodate tests which utilize sound[12] (fetal sound acceleration test), tactile arousal (fetal arousal acceleration test), or other tests along similar lines.

In conclusion, the A/C ratio as a measure of the degree of reactivity of the FHR has been shown to be a sensitive method for the antepartum assessment of fetal well-being. Reactive ratios were associated with a favorable outcome whereas nonreactive ratios were associated with a less favorable outcome. All FMAT's undertaken within a week of positive OCT's were nonreactive. The finding, however, of a number of nonreactive ratios in patients who had a favorable outcome suggests that the test is more suitable as a screening procedure to select candidates for an OCT. Exceptions may be made in view of the findings reported here suggesting that the FMAT may be more sensitive than the OCT. Decisions to terminate pregnancy when the FMAT is nonreactive and the OCT is negative may in selected circumstances be considered appropriate. Examples of such clinical conditions would be patients who manifest a mature L/S ratio in addition to one or more of the following factors: strong clinical evidence for IUGR or LGA, abnormalities in estriol excretion patterns, meconium staining of amniotic fluid, or patients who demonstrate frequent and repeated nonreactive FMAT's.

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Fetal breathing movements in uncomplicated pregnancies

I. Relationship to gestational age

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Fetal breathing movements occur in uncomplicated gestations. The relationship of fetal breathing movements recorded in 30 min sessions to gestational age and blood glucose levels is described. A total of 142 recording sessions were obtained from 45 gravid women with uncomplicated pregnancies from 24 to 41 weeks' gestation. There was a significant increase in the proportion of time spent in fetal breathing as gestational age increased. Glucose levels in a normal range (70 to 120 mg/100 ml) at the time of the recording sessions showed no correlation with the proportion of fetal breathing time. (AM. J. OBSTET. GYNECOL. 134:5-4, 1979.)

FETAL BREATHING (FB) movements have been documented in both animal and human gestations. In animal models, FB movements occurred during fetal activity similar to rapid eye movement sleep.[1, 2] Many studies have shown the effects of hypoxia, hypercapnia, and medications on FB movements.[3] In human gestation, it is known that the administration of glucose to the mother is followed by an increase of the time spent in FB.[4, 5]

Noninvasive A-scan, Doppler, and real-time B-scan ultrasound techniques all have been used to record indications of human FB movements. The real-time B-scan imaging system* provides an especially consistent presentation of these movements.[3]

In order to assess the value of FB movement observations in clinical fetal medicine, an understanding of the natural history of their occurrence in uncomplicated gestation is necessary. This report presents data on the relationship between gestational age, maternal blood glucose levels, and the amount of FB observed.

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**Advanced Diagnostic Research, Inc., Tempe, Arizona.*

Population

The population consisted of 45 Caucasian gravid women with singleton uncomplicated pregnancies as judged by criteria similar to those of Goodwin and associates.[6] Three breech presentations were included. Maternal age ranged from 19 to 36 years with a mean of 27 ± 3.8 (S.D.) years. Neonatal weights ranged from 2,480 to 4,150 grams with a mean of 3,302 ± 388 (S.D.) grams. There were 20 female and 25 male infants. Gestational age (GA) at delivery ranged from 36 to 42 weeks with a mean of 39.5 ± 1.5 (S.D.) weeks. All 1 min Apgar scores were 5 or greater and all 5 min Apgar scores were 8 or greater. There was one case of intrapartum fetal distress due to apparent occult umbilical cord prolapse. None of the women were in labor during the recording sessions. No patient was delivered within 48 hours of a study session.

Method

Study sessions were approximately 30 min (mean 27 min, median 30 min) at specified times in the morning or afternoon. A linear-array transducer system* (2.25 MHz) was used to produce a longitudinal real-time B-scan image including the fetal thorax and abdomen. Patients were placed in the semi-Fowler position to avoid supine hypotension. No hypotension was noted during the recording sessions and the stabilization period was 10 min. During each recording session, the transducer was moved to maintain consistent orientation of the fetus for visual interpretation of FB

*Advanced Diagnostic Research, Inc.

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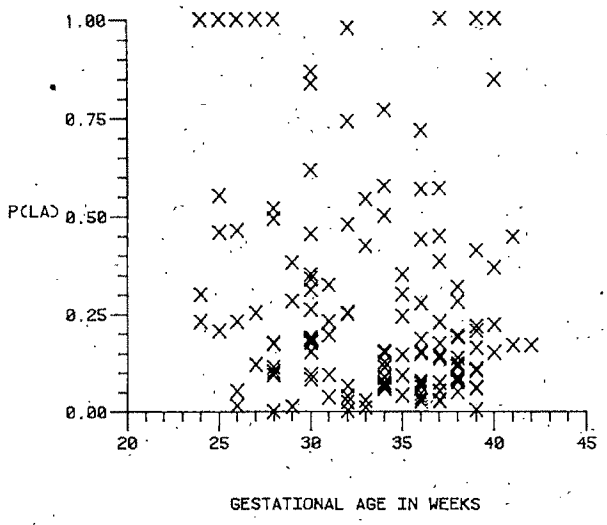


Fig. 1. Proportion of time spent in longest apnea versus gestational age in weeks.

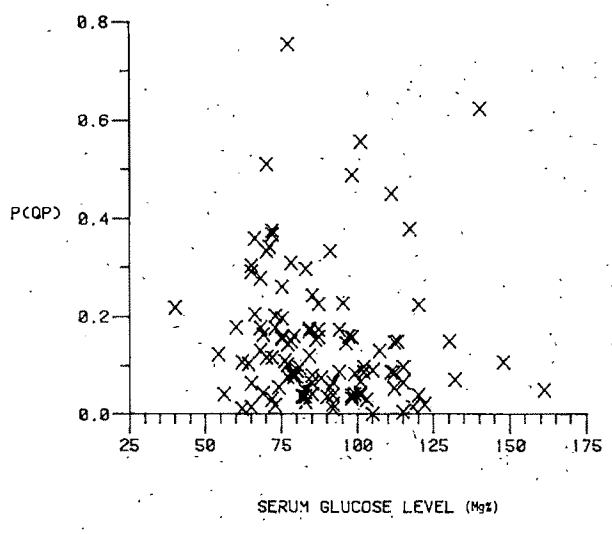


Fig. 2. Proportion of time spent in the longest period of neither breathing nor moving versus blood glucose level.

movements. A blood glucose level was determined by the glucose oxidase method at the beginning of each session. A continuous videotape record of the real-time B-scan image was made of each study session. The videotape was replayed and manually coded onto a polygraph record indicating FB, other fetal movement, and artifact (due to transducer or maternal movement).

The records were analyzed and the following measurements made: total examination time (TT), total FB time, total other fetal movement time (M) (not including FB), longest quiet period (QP), and the longest apnea period (A). Other fetal movement time was defined as documented movement time during which breathing activity could not be determined. A quiet period was defined as a period with no FB or other fetal movement. Apnea was defined as an interval (more than 6 sec) between observed fetal breathing episodes. An apnea interval might include fetal movements other than FB.

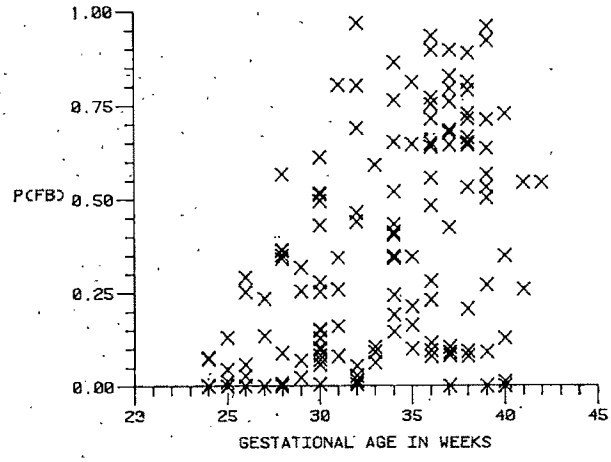


Fig. 3. Proportion of time spent in fetal breathing activity versus GA.

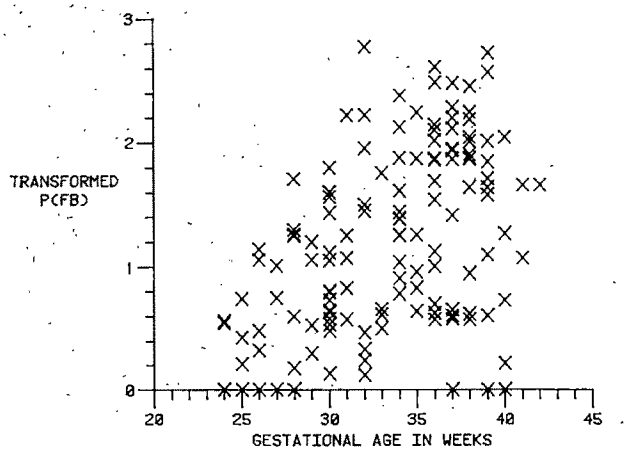


Fig. 4. Transformed proportion of time spent in fetal breathing versus GA.

Observations were made from 24 weeks' gestation to delivery. Gestational age was verified by examination of the neonate after birth.

Results

Data obtained from 142 examinations on the 45 patients were analyzed. Because of variation in total examination time, variables of interest were considered as proportions (P).

The three variables considered were:

1. P(FB) = FB/TT-M—the proportion of the examination time when all fetal activities were discernible that was spent in breathing activity.
2. P(QP) = Q-P/TT-M—the proportion of the examination time when all fetal activities were discernible that was spent in the longest period of neither breathing nor moving.
3. P(LA) = LA/TT—the proportion of the exami-

Table I. Proportion of time spent breathing in various GA categories

GA (wk)	*Examinations (N)*	*P (FB) (mean ± SE)*
24-29	33	0.12 ± 0.03
30-34	46	0.33 ± 0.04
35-39	54	0.51 ± 0.04

nation time in the longest observed period of apnea.

Comparison of morning and afternoon values for all proportions showed no statistical differences. In subsequent analyses, the data were considered as a single group.

Fig. 1 shows P(LA) versus GA. There was no obvious relationship although the rank-order correlation was − 0.21, suggesting a slight inverse relationship. There was a wide variation in P(LA) and in the actual values of LA at all gestational ages. In Nine sessions apnea was present during the entire session. There was an insignificant relationship between P(LA) and blood glucose values (rank-order correlation = − 0.24).

No strong relationship exists between P(QP) and GA (rank-order correlation = − 0.06). Fig. 2 shows P(QP) versus blood glucose levels. There was no clear relationship although the rank-order correlation was −0.22, again suggesting an inverse relationship.

Fig. 3 shows a plot of P(FB) versus GA. There was a clear positive relationship with increasing variability in P(FB) as GA increases. The rank-order correlation was 0.46. Table I shows the average P(FB) as various GA categories.

Because P(FB) is a proportion, the usual regression techniques were not appropriate, so further investigation of the relationship between P(FB) and GA was done with a standard transformation for proportions (2 arc sine $\sqrt{\ }$) and weighted regression.[8] Fig. 4 shows a plot of the transformed P(FB) versus GA. The linear term ($F = 34.9$) was significant ($p < 0.001$) and the nonlinear term ($F = 1.2$) was not, indicating that a simple linear relationship between the transformed P(FB) and GA holds. The addition of the blood glucose levels to the regression equation did not improve the fit.

Comment

A positive correlation exists between the proportion of time spent in FB activity and advancing GA. The relationship is most clear for GAs of less than 32 weeks (refer to Fig. 3). The premature neonate demonstrated developmental changes in breathing patterns as GA advanced.[7] It is reasonable to expect that similar developmental changes are expressed in the intrauterine breathing activity. The relationship between the proportion of time spent in FB and GA may reflect respiratory neuroregulatory control maturation.

An intravenous glucose load administered to the mother increased the occurrence of FB.[4] Also, an oral glucose load has been shown to produce a similar effect.[5] The blood glucose level prior to the recording session was recorded in order to determine any relationship between glucose level and the proportion of time spent in FB with respect to GA. Over a normal glucose range, no significant correlation between blood glucose levels and the proportion of time spent in FB was observed.

Conclusions

There is a significant relationship between the proportion of time spent in FB and GA. This relationship is most obvious at less than 32 weeks' gestation. Maternal blood glucose levels in a normal range at the time of the recording sessions show no significant correlation with the proportion of time spent in breathing activity.

There is an increasing variance in the proportion of time spent in FB as GA increases. It is important to recognize this large degree of variability in the occurrence of FB activity in uncomplicated patients when one considers the study of FB movements as a clinical indicator of fetal condition.

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Prenatal diagnosis of Tay-Sachs disease: Studies on the reliability of hexosaminidase levels in amniotic fluid

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Measurement of hexosaminidase A activity in amniotic fluid was found to be a reliable diagnostic test in the prenatal diagnosis of Tay-Sachs disease. Including normal control specimens, analysis of 39 amniotic fluid samples have correctly predicted the condition of the fetus or, in pregnancies not yet come to term, have been in agreement with results from cultured cell extracts. In each case where both fluid and cultured cell extracts were analyzed, the results were in agreement. Analyses were performed by means of Cellogel, starch gel electrophoresis, polyacrylamide gel electrophoresis, or heat inactivation. (AM. J. OBSTET. GYNECOL. 134:547, 1979.)

THE MEASUREMENT of hexosaminidase A (hex A) activity in amniotic fluid and cultured amniotic fluid cells is the standard procedure for in utero diagnosis of Tay-Sachs disease. Although the hex A deficiency diagnostic of the disease has been demonstrated in both fluid and cultured cell extracts,[1, 2] the reliability of the enzyme levels in fluid has not yet been firmly established and the use of cell extracts is generally advocated.[3, 4]

The results of 27 prenatal diagnoses in our laboratory support those of an earlier report[2] suggesting that amniotic fluid and cultured cell extracts are equally reliable. The presence or absence of hex A in fluid was clearly discernible, and the reliability of this determination seems adequate to warrant use of fluid for early diagnosis while growth of cultured cells for confirmation is awaited. The use of *both* fluid and cell extracts is still strongly indicated because enzymes derived from two different sources provide a valuable cross-check as an added measure of safety.

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Methods

Preparation of samples. Approximately 15 ml samples of blood-free amniotic fluid were centrifuged at 300 × g to collect the cells for culturing. The supernatant fluids were tested with urinalysis reagent strips* to verify that the samples were not maternal urine[5] and recentrifuged at 25,000 × g at 4° C for 20 minutes. Five milliliters of the supernatant fluid were concentrated approximately 25-fold in a Minicon B-15 concentrator† at 4° C and used directly for electrophoresis or stored frozen.

Amniotic fluid cells were cultured in Eagle's basal medium (supplemented with 20% fetal calf serum), washed, and suspended in 100 to 200 μl of 0.9% NaCl. Extracts were prepared by freezing and thawing the cell suspension five times. The extract was centrifuged at 1,000 × g for 10 minutes and the cell-free supernatant fluid was used for electrophoresis without further treatment.

Substrate. A 3 mM solution of 4-methylumbelliferyl-N-acetylglucosaminide in 6.1 mM citrate 10 mM phosphate buffer pH 4.4 (C-P buffer) was used as substrate in all experiments.

Electrophoresis. Cellogel strips (5.7 × 14 cm) containing 10 μl of each sample were electrophoresed for 2 hours in 0.04M potassium phosphate buffer, pH 6.5, according to manufacturer's instructions. Strips were dipped in substrate for 15 seconds, incubated in a moist chamber, and viewed under ultraviolet light.

*Multistix, Ames Co.
†Amicon Corp.

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Table I. Hexosaminidase A activity in amniotic fluid and cultured cell extracts from pregnancies at risk for Tay-Sachs disease

Set and No.	*Amniotic fluid*				*Cultured cell extract*			*Confirmation of prenatal diagnosis after birth or abortion*
	PAGE (% Hex A)*	*Starch gel*	*Cellogel*	*Heat inactivation 52° C (% Hex A)*	*PAGE (% Hex A)*	*Starch gel*	*Cellogel*	
Set A:								
1	6.3	+	+			+	+	Normal
2	2.4	+	+	5.7		8%†	+	Normal‡
3	0	0	0	3.9		0	0	TSD
4	0	0	0	3.1			0	TSD
5	16.7	+	+	7.4		+		Normal
6	0	0	0		0			TSD
7	10.7	+	+	8.3	19	+		Normal
8		+	+	5.8	41	+	+	Normal
9	0	0	0	3.3		0		TSD
10	11.5	+	+	15.8		+		Normal
11	14.4	+	+	8.4	67	+		Normal
12	0	0	0	7.2	0			TSD
13	8.4	+	+	7.6		+		Normal
14	0	0	0	5.4	0			TSD
15	0	0	0	4.3	0			TSD
16	14.7	+	+	10.8	39			Normal
17	24	+	+	10.1	36			Normal
18	8.2	+	+	8.8	33			Normal
19	10.5	+	+	9.9	29			Not delivered
20	23	+	+			+		Not delivered
Set B:								
1	31							Normal
2	7.6			16.3				Normal
3	19.3							Normal
4	15.5							Normal
5	0	0	0	3.2				TSD
6	10							Normal
7	17							Normal
Set C:								
1	20	+	+	15.4				Normal
2	19	+		15.4				Normal
3	15.7	+						Normal
4	24.5	+	+					Normal
5	15.5	+						Normal
6	26.3	+	+	20.1				Normal
7	32.5	+	+	16.8				Normal
8	17.1			12				Normal
9	27.3	+	+	18.6				Normal
10		+	+	11.8				Normal
11		+	+					Normal
12	39.7	+	+					Normal

*Percentages were calculated by measuring the area under the peaks obtained with PAGE as in Fig. 1.
†Approximate quantitation of fluorescent bands from gel.
‡See discussion in text.

Starch gel electrophoresis was performed according to the method of Smithies.[6] Gels (14%) were prepared in 5 mM citrate 17.8 mM phosphate buffer pH 6.2. Fifty microliters of each sample were applied to the slots and the gels were electrophoresed for 18 hours at a constant current of 40 mA at 4° C in 0.04M citrate and 0.143M phosphate buffer, pH 6.2. Gels were sliced horizontally and covered with a sheet of filter paper moistened with substrate. After incubation at 37° C for 20 minutes, enzyme bands were visible under ultraviolet light.

Polyacrylamide gels (PAGE) and buffers were prepared according to the method of Friedland and associates.[7] Twenty microliters of sample were mixed with 40 μl of 40% sucrose solution and 20 μl of 0.1M phosphate buffer, pH 7, containing 0.9% NaCl. The mixture was electrophoresed at 2.5 mA per tube for 70 minutes at ambient temperature. Gels were frozen, sliced, and assayed by suspending each slice in 100 μl of C-P buffer to which was added 100 μl of substrate. After incubation for 30 minutes at 37° C, the reaction was stopped with 4.85 ml of 0.17M glycine-carbonate

buffer pH 10, and free 4-methylumbelliferone was measured fluorometrically.

Heat inactivation was performed essentially as described by Kaback.[8] Samples were prepared by diluting 200 μl of unconcentrated amniotic fluid with 1.2 ml of C-P buffer containing 5.75 mg/ml hexosaminidase-free human serum albumin. Inactivation was done under three conditions, 50° C, 2 hours; 52° C, 2 hours; and 60° C, 5 minutes.

Normal and affected control samples were simultaneously run with all samples.

Results

Since 1975, 20 pregnancies at risk for Tay-Sachs disease have been monitored by measuring hex A levels in amniotic fluid and in cultured cell extracts. Samples were analyzed by PAGE, starch gel electrophoresis, Cellogel electrophoresis, or heat inactivation. In every case the results of amniotic fluid and cultured cell extracts were in agreement (Table I, Set A). Seven cases were diagnosed as affected since no trace of hex A was found by any electrophoretic procedure. Thirteen cases showed the unambiguous presence of hex A. Confirmation of all diagnoses was made by measuring hex A levels in cord blood at birth or in tissue extracts of abortuses.

A second set of fluids was tested retrospectively from prenatal diagnoses prior to 1975 when only cultured cell extracts had been used (Table I, Set B). These fluids, which had been stored frozen from 2 to 4 years, still yielded the correct results. Finally, normal (from nonJewish patients) control samples are shown in Table I, Set C. In every case, analysis of the fluid correctly diagnosed the condition of the fetus or, in the two pregnancies not yet come to term (Nos. 19 and 20), have been in agreement with results from cell extracts.

Fig. 1 shows four examples of results obtained with PAGE of amniotic fluid. In all fluids examined by this method, the presence or absence of hex A peak was equally unequivocal. Less clear-cut distinction was obtained from heat inactivation studies on the amniotic fluid samples of set A which at 52° C gave hex A values for affected cases ranging from 3.2 to 7.2 despite the fact that all three electrophoretic procedures showed no trace of hex A for the same samples. We interpret this to mean that the residual hex A activities indicated in the affected fetuses by heat inactivation are spurious values resulting from the usually unavoidable destruction of some hex B or I, which by definition is then designated as hex A. This interpretation is based on our observation that regardless of how conditions of inactivation are varied (pH, temperature, ionic strength, etc.), when adequate destruction of hex A is

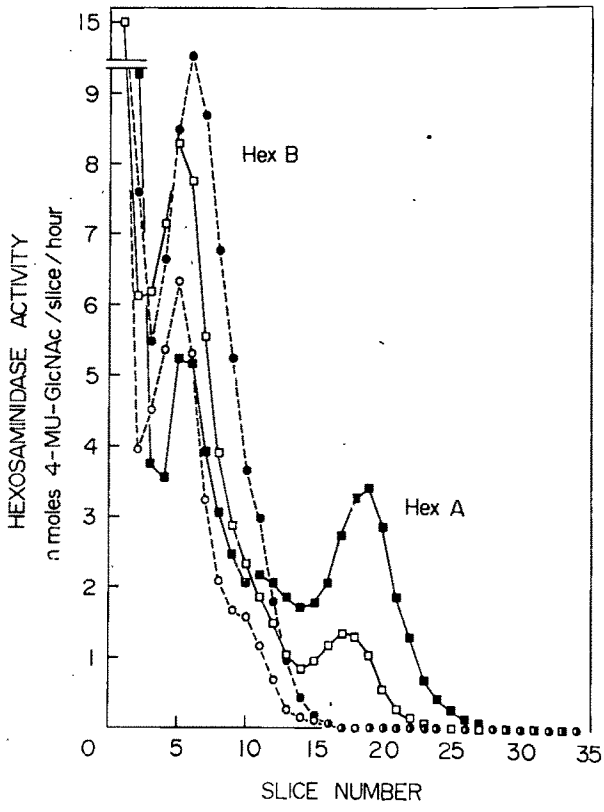


Fig. 1. Polyacrylamide gel electrophoresis showing hexosaminidases in four amniotic fluid samples. Normal enzyme patterns are represented by squares (-□-□-□-□-□-, -■-■-■-■-) and enzyme patterns from affected pregnancies are represented by circles (-o-o-o-o-o-, -●-●-●-●-●-). The peak labeled *HEX B*, consisting of both hex B and I, is prominent in all samples. The more anodic hex A peak is absent in fluid from affected pregnancies.

achieved, some slight inactivation of the heat-stable forms usually also occurs. When samples were inactivated at 50° C all hex A values were lower by an average of 33%, and while some of the affected cases did then show 0% hex A, there was still overlap between some normal and affected subjects and the discrimination was not improved. Heating at 60° C for five minutes gave the poorest discrimination.

Comment

The data show that analysis of amniotic fluid by electrophoretic methods permitted unambiguous determination of the presence or absence of hex A. Affected fetuses had a complete deficiency of hex A activity while those unaffected had clearly demonstrable amounts of hex A albeit much less than those found in fibroblasts and other tissues. Since two thirds of the unaffected fetuses of pregnancies at risk are carriers, the mean hex A values of this group are even lower than those of normal control subjects. The low hex A

activity makes its detection more difficult and requires greater care in technique and choice of methods. Because of this low activity we do not rely on the heat inactivation method which may yield spurious values which at times are difficult to distinguish from real, but low, hex A values of fluid. However, this limitation does not detract from the usefulness of the method for measuring hex A in cell extracts and other tissues which contain high hex A activity.

A particularly stringent test of the reliability of fluid was encountered in Case 2 (Table I) where hex A in both fluid and cell extracts was definitely present but disturbingly low (2.4 and 8%, respectively). The fetus was eventually diagnosed as not affected with classical Tay-Sachs disease (but because of the low hex A levels the possibility of a late onset form was not excluded) and the pregnancy was continued to term. At birth serum hex A values were about one third the mean for nonaffected children of at risk pregnancies, so the unusually low hex A activity in fluid and cells at diagnosis were, in retrospect, an accurate reflection of the low enzyme levels later found at birth. However, at last examination at 23 months the child showed normal development and was free of any symptoms.

In addition to the appropriate analytic techniques and controls, and rigid adherence to proper methodology,[9] other requirements for the successful use of amniotic fluid for prenatal diagnosis are that the sample be free of maternal blood, that it be kept cold or frozen to minimize loss of hex A activity, that the possibility of maternal urine be eliminated, that bacterial contamination be prevented, and that the fluid be sufficiently concentrated.

We wish to express our thanks to Marie Barr, Cheryl Fisher, and Martha Young for providing the cultured amniotic fluid cells, and to Kathleen Grolsko for assistance in preparation of the manuscript.

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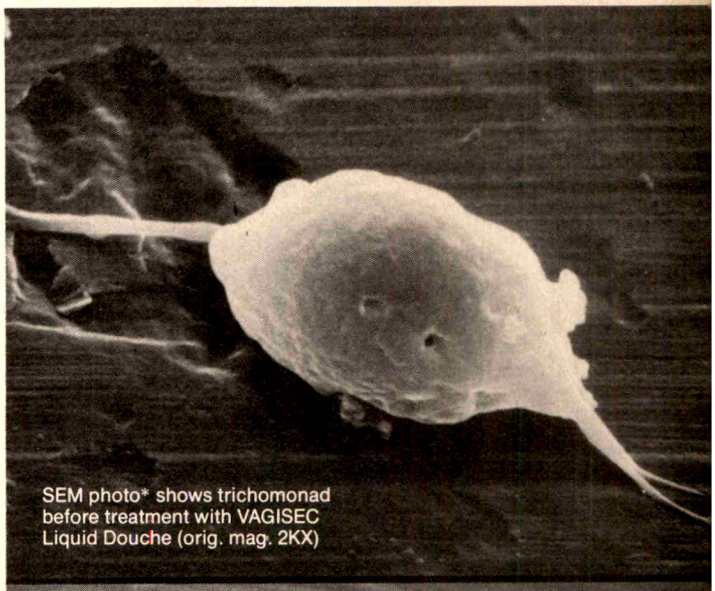
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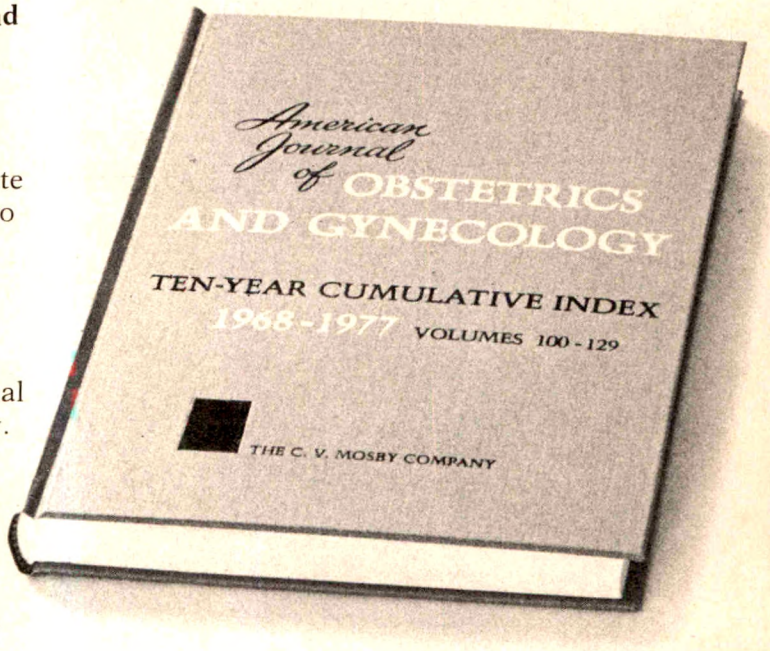
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GYNECOLOGY

Correlation between retinal and pelvic vascular status: A determinant factor in patients undergoing pelvic irradiation for gynecologic malignancy

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The degree of arteriolar sclerosis in pelvic vessels has previously been shown to be related to the incidence of radiation-related enteric and genitourinary injury. Retinal vessel changes were compared to pelvic vascular changes in 48 patients, half of whom were either diabetic or hyptertensive. There was an absolute correlation between retinal vessel changes and bowel or cervicovaginal vessel changes in 74% of the cases, and only one patient had a marked (more than one grade) discrepancy between retinal and pelvic vascular status. The findings of this investigation suggest that funduscopic examination of the retina can provide useful information concerning the extent of vascular disease in structures normally present in the field of pelvic irradiation.
(AM. J. OBSTET. GYNECOL. 134:551, 1979.)

ONE OF THE CHALLENGES of pelvic radiation therapy has been to deliver tumoricidal doses to the site of malignancy while minimizing the dose given to adjacent radiosensitive normal tissues.

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To achieve this goal, sophisticated treatment planning methods have been developed utilizing computerized methods as well as radiologic scanning techniques for localization of tumors and normal pelvic structures. An important factor in the response of normal tissues to radiation has been the vascular status of the patient. Radiation has been shown to cause capillary endothelial proliferation, changes in vascular permeability, and luminal stenosis with consequent decrease in blood flow.[7, 12, 13] When these radiation-related changes are superimposed upon underlying vascular disease, tissue hypoxia and necrosis occur. In previous investigations from this institution,[14, 15] the incidence of major enteric and urinary tract complications following pelvic irradiation for cervical cancer

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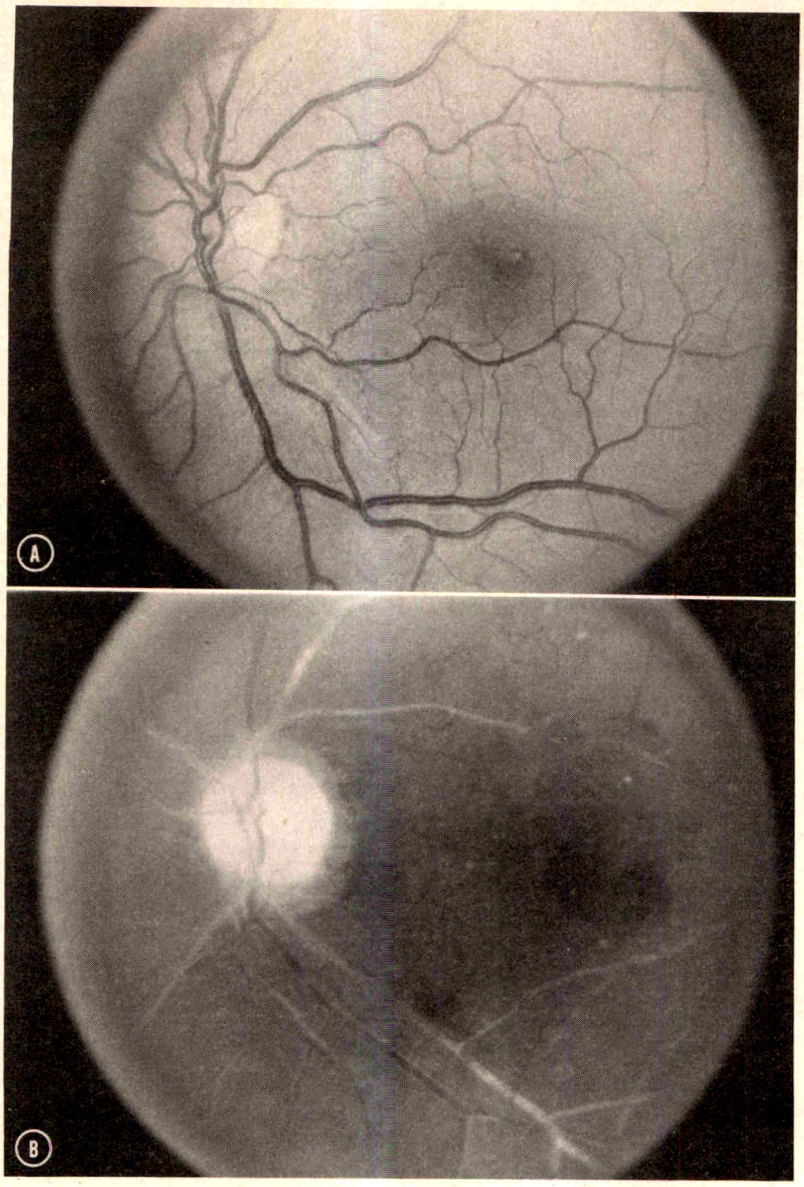


Fig. 1. *A*, Normal (grade 0) retinal vessels with no evidence of arteriolar sclerosis. *B*, Marked retinal arteriolar narrowing (grade 4 changes).

were shown to be significantly increased in patients with hypertension or diabetes mellitus.[14, 15] It was suggested that the underlying angiopathy associated with these diseases when added to radiation-induced arteriolar damage was responsible for the increased incidence of tissue injury and fistula formation.

The present study was undertaken in order to determine the correlation between retinal vessel changes as observed by funduscopic examination and pelvic vascular status. Specifically, changes in the retinal vessels were compared to changes in the small arterioles of organs normally present in the field of pelvic irradiation.

Material and methods

Subjects for this investigation included 48 patients who were admitted to the Gynecology or Gynecologic Oncology Services at the University of Kentucky Medical Center from 1972 to 1977. Hypertension was defined as a systolic pressure of more than 140 mm Hg or a diastolic pressure of over 90 mm Hg. The diagnosis of diabetes mellitus was made if the 2 hour value of the glucose tolerance test was greater than 140 mg per 100 ml. Funduscopic examination and retinal photography were performed on all patients and fluorescein angiography was utilized in selected cases. Retinal vessels were classified according to the system proposed

by Ballantyne and Michaelson[2] (Table I). This classification varied from normal vessels with no evidence of arteriolar sclerosis (Fig. 1, *A*) to extensive arteriolar sclerosis with an arteriolar:venous ratio < 1:4 (Fig. 1, *B*). Within 3 weeks of retinal examination, all patients underwent surgical exploration with removal of bowel, bladder, ovary, uterus, or vagina. No patient had received prior radiation therapy or had a history of previous pelvic inflammatory disease. Small arterioles (<100 μ in diameter) in each of the organs removed were examined histologically without knowledge of the retinal vessel status of the patient and were classified according to the extent of luminal narrowing (Table II). Five to 10 vessels were examined from each specimen and Elastin van Gieson Stains were utilized in selected cases to outline arteriolar dimensions. Arterioles varied from no evidence of sclerosis and a lumen diameter:vessel diameter ratio > 1:2 (Fig. 2, *A*) to marked medial thickening and fibrinoid necrosis with a lumen diameter:vessel diameter ratio < 1:4 (Fig. 2, *B*).

Table I. Classification of retinal vessels

Grade	*Criteria*
0	No evidence of arteriolar sclerosis
1	Increased light reflex (arteriolar:venous ratio = 2:3)
2	Arteriovenous nicking or compression (arteriolar:venous ratio less than 1:2)
3	Copper wire changes (arteriolar:venous ratio less than 1:3)
4	Silver wire changes (arteriolar:venous ratio less than 1:4)

Table II. Classification of pelvic vessels

Grade	*Criteria*
0	No significant changes
1	Slight thickening of the media (lumen diameter:vessel diameter = 1:2)
2	Prominent medial thickening (lumen diameter:vessel diameter = 1:3)
3	Medial thickening with subintimal proliferation (lumen diameter:vessel diameter = <1:3)
4	Medial thickening with fibrinoid necrosis (lumen diameter:vessel diameter = <1:4)

Table III. Retinal vessel–pelvic vessel correlation

Vessel site	*Observations*	*Absolute correlation*	*±1 Grade correlation*
Cervicovaginal	42	32 (76%)	42 (100%)
Bowel	15	11 (73%)	15 (100%)
Other pelvic sites	30	22 (73%)	29 (97%)
Total	87	65 (74%)	86 (99%)

Results

Twenty-four of the 48 patients were either hypertensive or diabetic and there was equal distribution of these patients and normotensive patients in the various organ sites observed. Cervicovaginal vessels were evaluated in 42 cases, large or small bowel vessels in 15 cases, and vessels from various other organs including pelvic muscles, fallopian tube, or ovaries in 30 cases (Table III). There was no evidence of retinal or pelvic vascular abnormality in 92% of normotensive patients. Two of these patients had grade 1 retinal or pelvic vascular changes. Grade 1 to grade 4 vascular changes were noted in the pelvic or retinal vessels of 87% of hypertensive or diabetic patients. The remaining hypertensive patients had no histologic evidence of vascular abnormalities. There was absolute grade correlation between retinal and pelvic vessel changes in 74% of the cases. This correlation was essentially the same whether the patient was known to have vascular disease or was in the control group. There was agreement within ±1 grade in an additional 25% of the cases. There was a marked (>±1 grade) difference between retinal and pelvic vascular findings in only one patient. The statistical correlation between findings in retinal and pelvic vessels was calculated using both the Pearson Product Moment and chi-square systems. There was an overall correlation between retinal vessel and pelvic vessel changes of 0.88 which was significant at a level of $p < 0.001$. The specific correlations between vascular findings in the retina and those in the uterus, and bowel are illustrated in Figs. 3 and 4. The correlation between retinal and cervicovaginal vessel changes was 0.87 and between retinal and bowel vascular findings it was 0.89. Both these correlations were statistically significant ($p < 0.001$). There was also a significant correlation between changes in retinal vessels and in those from other pelvic organs including the ovary and fallopian tube.

Comment

There are much data in both experimental animals and man concerning the effect of gamma radiation on small vessels. Specifically, capillary endothelial proliferation, medial thickening, and increased vascular permeability have been demonstrated within 2 months following radiation.[12] With narrowing of the lumina of arterioles, there is decreased flow in the microcirculation, lowered oxygen tension and oxygen uptake rate, and initiation of anaerobic metabolism.[4] Increased vascular permeability often causes insudation of plasma constituents into the capillary wall with subsequent fibrinoid vascular necrosis and thrombosis.[10] Dutta,[5] using autoradiographic techniques, has demonstrated

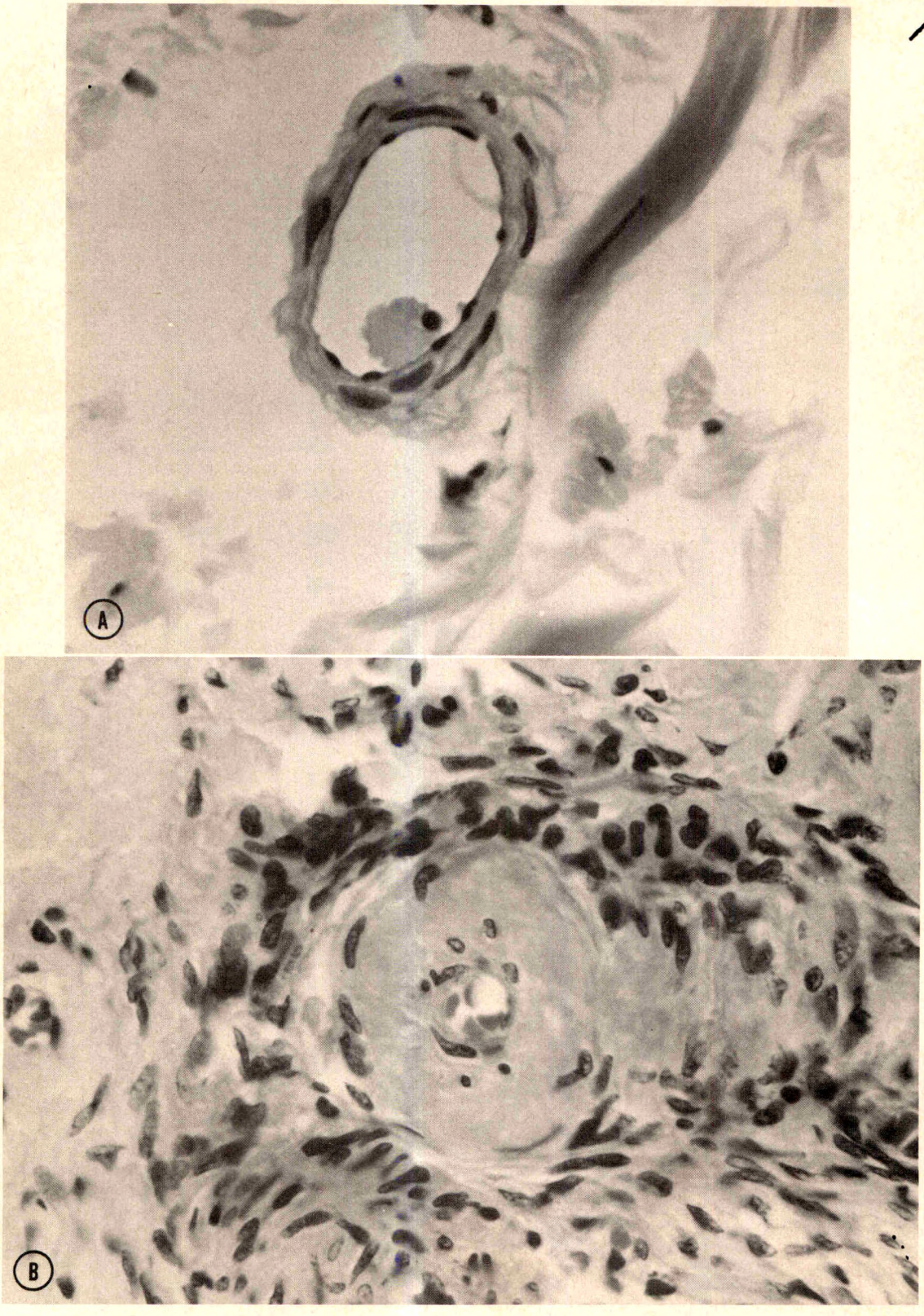


Fig. 2. *A*, Normal pelvic vessel with no evidence of luminal narrowing. (Hematoxylin and eosin. ×400.) Pelvic vessel with marked medial thickening (lumen diameter : vessel diameter = <1 : 4). Absence of fibrinoid necrosis places this vessel in grade 3 category. (Hematoxylin and eosin. ×400.)

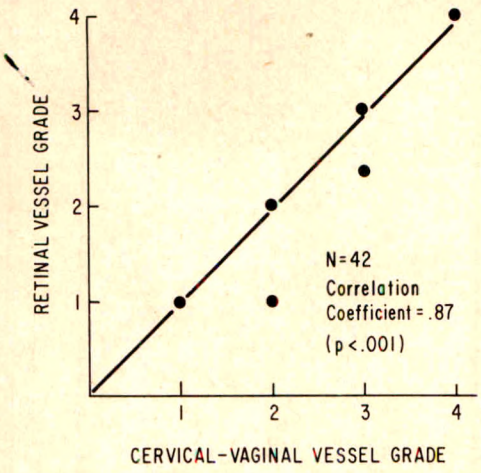


Fig. 3. Correlation between retinal vessel grade and cervicovaginal vessel grade.

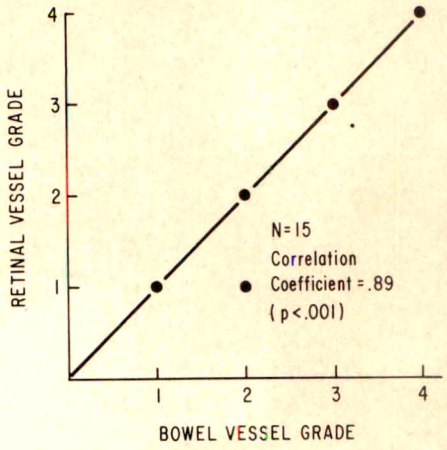


Fig. 4. Correlation between retinal vessel grade and bowel vessel grade.

that radiation causes increased sulfate metabolism in the wall of mesenteric arterioles and that these vessels are then more susceptible to damage by increased intravascular pressure often present in hypertension.

These experimental findings have been confirmed by clinical observations in patients undergoing pelvic irradiation for gynecologic malignancies. van Nagell and co-workers,[14, 15] for example, reported that the incidence of enteric and urinary tract fistula following irradiation for cervical cancer was significantly increased in patients with hypertension or diabetes when compared to patients with no pre-existing vascular disease. Furthermore, arteriolar medial thickening and luminal narrowing in the bladder and rectum was significantly more common in hypertensive or diabetic patients who had not received radiation therapy than in control patients. It was therefore suggested that the underlying microangiopathy present in patients with small vessel disease predisposed these patients to vascular damage following radiation therapy, ultimately leading to tissue necrosis and fistula formation. It was also postulated that patients with pre-existing vascular disease might benefit from greater fractionation of the total dose of pelvic irradiation, thereby allowing for increased normal tissue repair.

It is generally recognized that the extent of arteriolar sclerosis and luminal narrowing is related to both the severity and duration of hypertension or diabetes.[3, 11] When patients requiring radiation therapy for pelvic malignancy are first examined, it is often difficult to determine the extent or length of time they have had vascular disease. Previous investigations[6, 9] have indicated that there is a high degree of correlation between retinal vessel changes and those present in cerebral and peripheral arterioles. The data of the present study confirm these findings and indicate that retinal vessel changes are associated with similar changes in the small arterioles of the bowel and urogenital system. Since the primary goal of any treatment regimen is to achieve tumor control, greater dose fractionation should be considered only for those patients with severe sclerotic vascular changes who are at highest risk to develop radiation-related enteric complications. It is apparent from this and other investigations[1, 8] that funduscopic examination of the retina can provide useful information concerning the extent of vascular disease in structures normally present in the field of pelvic irradiation.

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Uterine leiomyosarcoma

A review of prognostic clinical and pathologic features

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A series of uterine leiomyosarcomas was reviewed in an attempt to assign prognostic significance to clinical and pathologic features. Extension of the sarcoma at the time of initial diagnosis was associated with a dismal outcome; no patient with disease beyond the confines of the uterus survived. Histologic grade was a useful prognostic feature, although low-grade sarcoma can be associated with metastases. Mitotic count was also useful in prognosis, although it did not correlate as well with clinical outcome as did histologic grade. There was no number of mitoses below which the diagnosis of leiomyosarcoma was excluded. (AM. J. OBSTET. GYNECOL. 134:557, 1979.)

INTERPRETATION OF LITERATURE describing the clinical behavior of uterine leiomyosarcoma has always been difficult because the reports do not agree on the histologic criteria necessary for diagnosis of the lesion. Indeed, Corscaden and Singh[1] stated that no combination of histologic features is reliable and that only the smooth muscle tumors that metastasize or that recur after excision can be considered as definitely malignant.

Two recent reports in which the clinical and pathologic data were reviewed in series of leiomyosarcoma have emphasized different criteria both for diagnosing the lesion and for estimating the behavior of the tumor. Kempson and Bari[2] stated, after review of the series of Taylor and Norris[3] as well as their own cases, that the sole criterion for malignancy in the absence of obvious vessel invasion or spread to contiguous organs is the mitotic count. Thus, all tumors with less than five mitotic figures (MF) per 10 high-power fields (HPF) are benign; all tumors with greater than 10 MF/10 HPF are malignant. They believe that these criteria are valid regardless of cellular atypia, pleomorphism, or the presence of giant cells. Kempson and Bari also defined an entity they called "smooth muscle tumors of uncertain malignant potential." These are tumors with less than 10 MF/10 HPF and are divided into four categories, consisting of those between 5 and 9 MF/10 HPF (with or without pleomorphism) and those between 1 and 4 MF/10 HPF (with or without pleomorphism). The probability of metastasis or recurrence decreases with decreasing mitotic count and lessening atypia. The total number of such cases in their series is small: seven cases between 5 and 9 MF/10 HPF and 10 cases between 1 and 4 MF/10 HPF.

Silverberg[4] believes that the mitotic count has some prognostic significance but poor diagnostic significance. The features that he believes determine malignancy are nuclear hyperchromatism and nuclear pleomorphism. Those that he considers helpful but not diagnostic are the presence of giant cells and nuclear inclusions. He does not demand any level of mitoses for the diagnosis of sarcoma and believes that even though a relationship may exist between mitotic index and outcome it is fallible and does not correlate as well as histologic grade with outcome. He believes that some insight into the behavior of leiomyosarcomas can be based upon a histologic grading system similar to that suggested by Spiro and Koss.[6] Silverberg's grading system is as follows:

Grade 1. Well-differentiated tumor with typical low-power appearance of benign myoma; bundles of cells are orderly, although there may be foci of hemor-

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rhage and necrosis; nucleus-to-cytoplasm ratio is increased and the nuclei have mildly atypical cytologic features.

Grade 2. The general architecture of a leiomyoma is still apparent but is both more cellular and more atypical; nuclear hyperchromasia and anisonucleosis are more pronounced. These cells approach the appearance of benign smooth muscle.

Grade 3. The tumors are clearly atypical but are still recognizable as smooth muscle in origin; the spindle shape of cells may be lost, and round or polyhedral shapes may appear; numerous bizarre cell forms are present.

Grade 4. The smooth muscle origin of the tumor is difficult to recognize; pleomorphism is extreme.

Each tumor is graded by its most anaplastic region. Photographs of specimens of each tumor grade may be seen in Silverberg's[4] report.

The purpose of the present study is threefold: (1) to review clinical and pathologic features of all leiomyosarcomas diagnosed at the Hospitals of The University of Texas Medical Branch at Galveston (UTMB) for the past 15 years, (2) to classify this series of tumors by both histologic grade and mitotic count and to attempt to correlate these indices with the clinical outcome, and (3) to combine information on tumors in our experience with data from other reported series that meet Kempson's criteria for "tumors of unknown malignant potential," in an attempt to determine prognostic factors in this subgroup of smooth muscle tumors.

Methods

The patients considered for the study were those recorded by the Tumor Registry at UTMB with the diagnosis of uterine leiomyosarcoma during the 15 year period 1963 to 1977. The clinical records and pathologic material from the patients identified by the Tumor Registry were reviewed. Twenty-seven cases were thought to represent true uterine leiomyosarcoma and were included in the study. Pertinent clinical features were extracted and the follow-up data and survival statistics were brought up to date as recently as possible.

Material for pathologic examination was available for review in 23 cases. The gross appearance of the tumor was abstracted from the data that had been recorded at the initial examination of the surgical specimen. The microscopic slides, identified only by hospital case number, were reviewed independently by each investigator. Special note was made of histologic grade, mitotic count, vascular invasion, type of tumor margin, number of giant cells present, and the evidence of hemorrhage or necrosis.

In 22 cases, only tissue taken from the uterus and primary uterine tumor was evaluated. In a single case, the uterine sample was supplemented with tissue from the metastatic focus.

The histologic grade was determined according to Silverberg's[4] criteria, as given above. Mitotic figures were counted by each observer in at least 30 high-power microscopic fields per slide on two separate occasions. The criteria used to identify a mitotic figure varied between examiners. Results of the microscopic interpretation were compared, and when a discrepancy in pathologic interpretation occurred the material was examined jointly to arrive at a final histologic reading. Mitotic counts were considered to be in agreement, except in those cases in which the discrepancy would result in assignment to different statistical groupings.

Clinical findings. Among the 27 patients evaluated, the median age at the time of diagnosis was 51 years, with a range from 30 to 67. Fifteen women were at or beyond menopause; 10, before menopause; and for two patients, the menstrual stage was not available. Only five patients had had no pregnancies, and 21 had had children, including six who had had eight or more births. Ten patients had had a total of 15 spontaneous abortions.

Nineteen patients have died of leiomyosarcoma, and eight patients either are living and free of residual tumor or have died of nonrelated intercurrent disease. Of the eight surviving patients, six have been observed for more than five years. The remaining two patients are well, without residual disease, after two years. None of the surviving patients have either persistent or metastatic leiomyosarcoma. The two groups do not differ significantly in age, menstrual status, or parity.

Abnormal uterine bleeding, either postmenopausal bleeding or metromenorrhagia, was by far the most common initial symptom (observed in 20 patients). Pelvic pain was reported by seven. A pelvic mass was discovered during physical examination in eight patients before the initial operation, but in only four were any symptoms referable to this mass. Three patients observed a mass, associated with both pain and bleeding abnormalities. One patient complained of an otherwise asymptomatic pelvic swelling. Pelvic relaxation with symptomatic cystocele occurred as an initial symptom in two patients.

In patients with more advanced disease, the most common clinical manifestation of extrauterine spread was a large pelvic mass with progressive involvement and entrapment of adjacent pelvic viscera. A large pelvic mass of this type was observed during the course of the disease in 12 of the 19 patients with extrauterine spread, in eight patients at the time of initial surgical exploration, and in four patients as a central recurrence which developed some time after extirpative pelvic surgery.

Table I. Histologic grading of leiomyosarcoma

Histologic grade	Total patients (No.)	Surviving (No.)	Died (No.)
1	7	6	1
2	6	1	5
3	8	1	7
4	2	0	2
Total patients	23	8	15

Table II. Outcome related to numbers of mitotic figures and numbers of giant cells

	Total patients (No.)	Surviving (No.)	Died (No.)
MF/10 HPF:			
0-4	4	1	3
5-9	7	6	1
10-14	3	0	3
15-19	3	1	2
20+	6	0	6
Total	23	8	15
No. of giant cells:			
None	13	7	6
Rare	3	0	3
Moderate	3	0	3
Abundant	4	1	3
Total	23	8	15

Table III. Relationship between histologic grade and giant cells

Histologic grade	Giant cells			
	None (No.)	Rare (No.)	Moderate (No.)	Abundant (No.)
1	7	0	0	0
2	3	2	1	0
3	3	1	2	2
4	0	0	0	2

Table IV. Survival data of patients with leiomyosarcoma

Years past diagnosis	Total patients (No.)	Surviving (No.)	Died	
			No.	%
0	23	23	0	100
1	23	17	6	74
2	23	13	10	57
3	21	7	14	33
4	21	6	15	29
5	21	6	15	29

Two patients are alive without recurrence at 2 years.

The lung was by far the most common site of distant metastases. Nine patients had lung metastases, four had bone metastases, two had liver metastases, and two had isolated metastases to the small bowel. The duration of symptoms was characteristically short, since symptoms typically were of such a magnitude as to require prompt medical intervention. Menorrhagia so severe as to require blood transfusion before initial diagnostic or therapeutic action occurred in 12 of 24 patients for whom this information is available.

Two patients had been treated for cervical carcinoma in the past with pelvic irradiation. The onset of uterine leiomyosarcoma followed radiotherapy by 29 years in one patient and by just 10 months in the second.

Pathologic observations

Gross appearance. In 15 patients, the tumors were confined to the uterus at the time of initial surgery and descriptions of the pathologic findings on gross examination were available in 12. In six of these patients, the uterus was enlarged and greater than 10 cm in length. In the remaining six patients, the uterus was normal in overall size, with a length from cervix to fundus of 10 cm or less. In all patients, the uterus had visible smooth muscle nodules, many nodules in seven patients and only a single nodule in five. In those patients with the disease confined to the uterus, the largest leiomyosarcoma measured 18 by 13 cm; the smallest, 0.5 by 0.5 cm. (Both occurred in multinodular uteri.) The extremes of tumor size in uninodular uteri were from 3 by 3 cm to 10 by 10 cm.

On cut section, the tumors were described as soft yellow to white nodules, which exhibited a whirling fibrous pattern. Typically, they bulged above the plane of section, and areas of necrosis were visible grossly in eight. All tumors greater than 6 cm in diameter exhibited evidence of hemorrhage and necrosis on gross examination.

Six of the cases of leiomyosarcoma were confined grossly to a single smooth muscle neoplasm or fibroid. The features of these tumors are described below.

Microscopic appearance. No uniform histologic pattern was displayed by these lesions. Even though all tumors were more cellular than the benign myoma, the degree of cellularity varied greatly. In addition, the tumors varied substantially in the degree of pleomorphism, the presence and degree of cellular and nuclear aberration, and the extent to which the individual cells were undifferentiated. As noted earlier, these features, along with individual cell morphology, are the basis for histologic grading (Table I). In seven of the 23 cases examined, the investigators initially were not in agreement about the histologic grade, but in no instance was the disagreement greater than a single grade.

Mitotic activity was evident in all tumors varying from 3 to 34 MF/10 HPF (Table II). The investigators disagreed initially about the mitotic count in eight of

Table V. Leiomyosarcoma confined to the uterus

Case No.	Size (cm)	Grade	MF (No.)	Giant cells	Outcome
Leiomysarcoma "in situ":					
1	0.5	1	6	None	Survived
2	8	1	5	None	Survived
Leiomyosarcoma confined to a myoma:					
3	10	3	6	Abundant	Survived
4	6	1	8	None	Survived
5	3.5	1	19	None	Survived
6	10	1	21	None	Died
Leiomyosarcoma confined to uterus and beyond a single smooth muscle neoplasm:					
7	1.5	1	5	None	Alive
8	5	1	4	None	Died of intercurrent disease
9	7	4	2	Abundant	Died (2 yr.)
10	10	2	5	None	Survived
11	12	2	3	None	Died (2 yr.)
12	—	4	30	Abundant	Died (4 yr.)

the 23 cases. In one case, the disagreement was greater than 15 MF/10 HPF, but in the remaining cases the disagreement was never of a magnitude greater than one statistical grouping.

Giant cells of two types were observed. The first was that cell type described as a symplastic cell, which appeared as an aggregate of smooth muscle nuclei, clustered in an irregular fashion, without distinguishing cell boundaries and displaying only minor gradations of nuclear hyperchromatism and pleomorphism. The morphologic relationship of these cells to smooth muscle nuclei is maintained. The second type of giant cell is characterized by densely straining, irregularly shaped masses of nuclear material displaying extreme pleomorphism. These two cell types frequently coexist. The quantitative distribution of giant cells of the type was determined for each group of patients (Table II). The presence of giant cells is closely associated with histologic grade (Table III).

Microscopic evidence of hemorrhage was observed in 11 cases and evidence of necrosis, in eight.

Outcome

The overall survival rate four years after diagnosis was 20% of the group at risk (Table IV). No patient who survived four years after initial diagnosis died of leiomyosarcoma.

As noted earlier, six leiomyosarcomas appeared on gross pathologic examination of the uterus to be a simple myoma or fibroid, and the malignant nature of the neoplasm was discovered only upon microscopic examination. With application of the criteria of Przybora[5] for the diagnosis of "leiomyosarcoma in situ" (that is, an area of sarcomatous tissue inside of a simple myoma without coexistent invasion elsewhere in the uterus), two cases were found in this series. Both tumors occurred as central sarcomatous change of a single myoma in a multinodular uterus. One myoma was intramural and less than 1 cm in diameter; the other was subserous and 6 by 8 cm in size. Both were well-differentiated neoplasms, classified as grade 1, and there was no distinct margin between the sarcomatous areas of the smooth muscle tumor and the surrounding, apparently benign myoma. No giant cells were present in these tumors. The mitotic index was 6 MF/10 HPF in the smaller and 5 MF/10 HPF in the larger. Both patients survived following simple hysterectomy. The histologic features of these two tumors have been compared to those of other leiomyosarcomas confined to the uterus (Table V).

Four additional tumors were noted to be confined to a single smooth muscle neoplasm or fibroid but did not fulfill the criteria for "leiomyosarcoma in situ," either because of microscopic invasion at the tumor margin or because benign leiomyomatous elements were not found surrounding the malignant area. These tumors were larger than the in situ neoplasms, ranging from 3 to 10 cm; two were pedunculated submucous tumors. Unlike the in situ tumors, the entire smooth muscle neoplasms were composed of sarcomatous tissue. Two of the tumors had pushing margins; the others demonstrated infiltration of tissue adjacent to the stalk of the pedunculated tumor. No consistent pattern of histologic grade, mitotic activity, or presence of giant cells was found among these specimens (Table V). One patient with tumor confined to a myoma died of disseminated sarcoma 18 months after hysterectomy.

Six tumors were confined to the uterus but did not present the gross pathologic appearance of a tumor arising in or confined to a single smooth muscle tumor. These tumors either were multifocal or had diffuse spread throughout the myometrium in what has been described as a mural leiomyosarcoma.[8] Mitotic counts tended to be low although one tumor (Case 12) had

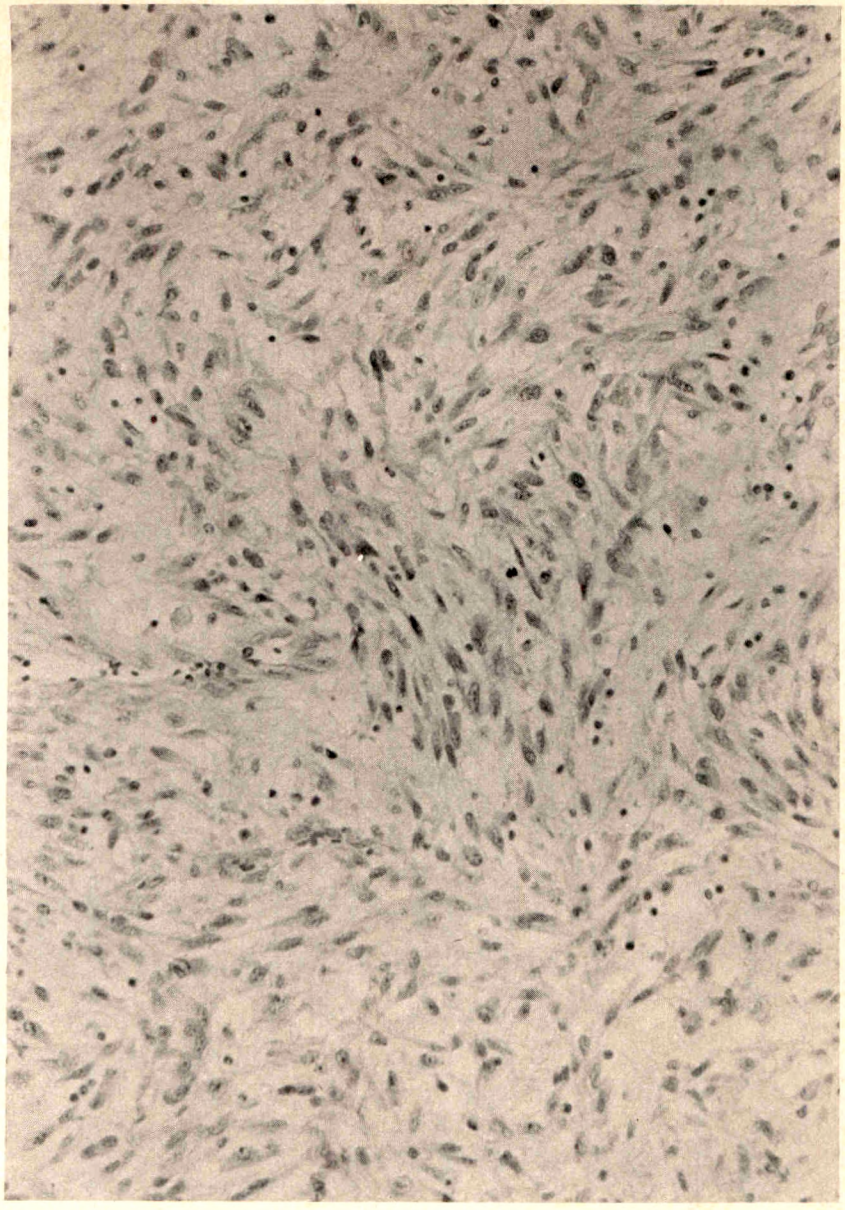


Fig. 1. Case 11. Grade 2 leiomyosarcoma with 3 MF/10 HPF. (Hematoxylin and eosin. ×25.)

pronounced mitotic activity (Table V). Three patients died of recurrent leiomyosarcoma; two of these patients had anaplastic tumors. A third patient (Case 11, Fig. 1), is of special interest in that she had relatively well-differentiated disease with a low mitotic count but died of widely metastatic disease within two years of initial hysterectomy. No spread beyond the uterus was apparent at the time of initial surgery, but she had a large 12 by 8 cm tumor mass penetrating the posterior uterine wall.

No patient with tumor beyond the uterus at the time of initial exploration survived. These patients were treated variously with simple hysterectomy, both alone and with radiotherapy, extended hysterectomy, irradiation alone, and various chemotherapeutic regimens. It is difficult to assign significance to any modality of therapy because of the small, heterogeneous groups involved.

Comment

The strong influence of the extent of the disease at the time of initial extirpative surgery is again obvious in this series of patients (Table VI). The dismal outcome of the 11 patients with sarcoma beyond the uterus is in sharp contrast to the 67% survival rate in the 12 patients with Stage I disease. One possible explanation for this sharp drop in survival is that first suggested by Corscaden and Singh[1] in their review of this phe-

Table VI. Relationship between outcome and stage

Stage	Total (No.)	Died	Survival	
			No.	%
I:	12	4	8	67
In situ	2	0	2	100
In myoma	4	1	3	75
Beyond myoma	6	3	3	50
II	0	0	0	0
III	5	5	0	0
IV	6	6	0	0

Table VII. Extent of disease related to histologic grade and mitotic activity

	Disease confined to uterus		Disease extended beyond uterus	
	Surviving (No.)	Died (No.)	Surviving (No.)	Died (No.)
Histologic grade:				
1	6	1	0	0
2	1	1	0	4
3	1	0	0	7
4	0	2	0	0
MF/10 HPF:				
0-4	1	2	0	1
5-9	6	0	0	1
10-14	0	0	0	3
15-19	1	0	0	2
20+	0	2	0	4

nomenon. A large proportion of the 12 patients in this group with Stage I disease may not have had a uterine sarcoma at all, but rather an incorrectly diagnosed cellular leiomyoma or degenerative changes in a benign myoma that appeared anaplastic. There are some data from our series that could be used to support this suggestion.

If the patients are divided into three groups, those with tumor confined to the uterus and surviving, those with tumor confined to the uterus who have died, and those with tumor beyond the confines of the uterus who have died, a cluster of patients with grade 1 tumor occurs in the first group (Table VII). Only a single patient with well-differentiated tumor died of the sarcoma, and no patient with well differentiated disease had extrauterine spread. Grade 1 anaplasia in our hands may be insufficient evidence to warrant a diagnosis of malignancy. The sole patient who died of low-grade sarcoma (Case 6) had pronounced mitotic activity with 21 MF/10 HPF. She developed pelvic and pulmonary recurrences within six months of hysterectomy and surgical removal of a tumor which was presumably confined to a fibroid.

Correlation of mitotic indices with the same three patient groups (Table VII) does suggest a relationship to eventual outcome, even though this relationship is

Table VIII. Extent of disease related to greatest mitotic activity in a single field

MF/HPF	Disease confined to uterus		Disease extended beyond uterus	
	Surviving (No.)	Died (No.)	Surviving (No.)	Died (No.)
1	2	0	0	1
2	4	0	0	3
3	1	1	0	1
4	0	2	0	1
5	0	0	0	0
6	1	0	0	2
7	0	0	0	1
8	0	1	0	0
9	0	0	0	0
≥10	0	0	0	2

not as pronounced as that between tumor grade and outcome. Two cases require additional comment. The patient of Case 9 (Fig. 2) had a 7 cm tumor confined to the uterus with only 2 MF/10 HPF and yet she died of the tumor. This tumor, however, displayed pronounced anaplasia with numerous bizarre nuclear forms, and the counting of mitotic figures depended upon the interpretation of the bizarre nuclear patterns. The difficulty in distinguishing mitoses from pyknotic nuclei, polymorphonuclear leukocytes, or small cell fragments folded upon themselves has been commented upon by others.[2, 7] The other patient (Case 11) who had a grade 2 neoplasm with 3 MF/10 HPF, did not display this confusing anaplasia. Special note is made of this case to illustrate that a moderately well-differentiated tumor with low mitotic activity which is confined to the uterus can recur, metastasize, and result in a fatal outcome.

Our data were re-examined and an attempt was made to correlate survival with the greatest number of mitoses observed in any single field (Table VIII). It is obvious that this measure of mitotic activity adds little information about tumors which have spread beyond the uterus at the time of initial diagnosis. Among patients with Stage I disease, there was no clear separation of patients into two groups based on survival and mitoses. There remains a cluster of patients who survived with tumors demonstrating low mitotic activity by this criterion. Attention is again directed toward Case 11 as an example of a tumor with low mitotic activity, which metastasized and resulted in the death of the patient. This tumor displayed a single field with four mitotic figures. As a tumor with a behavior different from that which might be expected, based upon its mitotic index, this tumor was extensively counted. Initially, over 100 consecutive high-power fields failed to demonstrate any area with greater than 2 MF/HPF. A single field with four mitoses was later located during

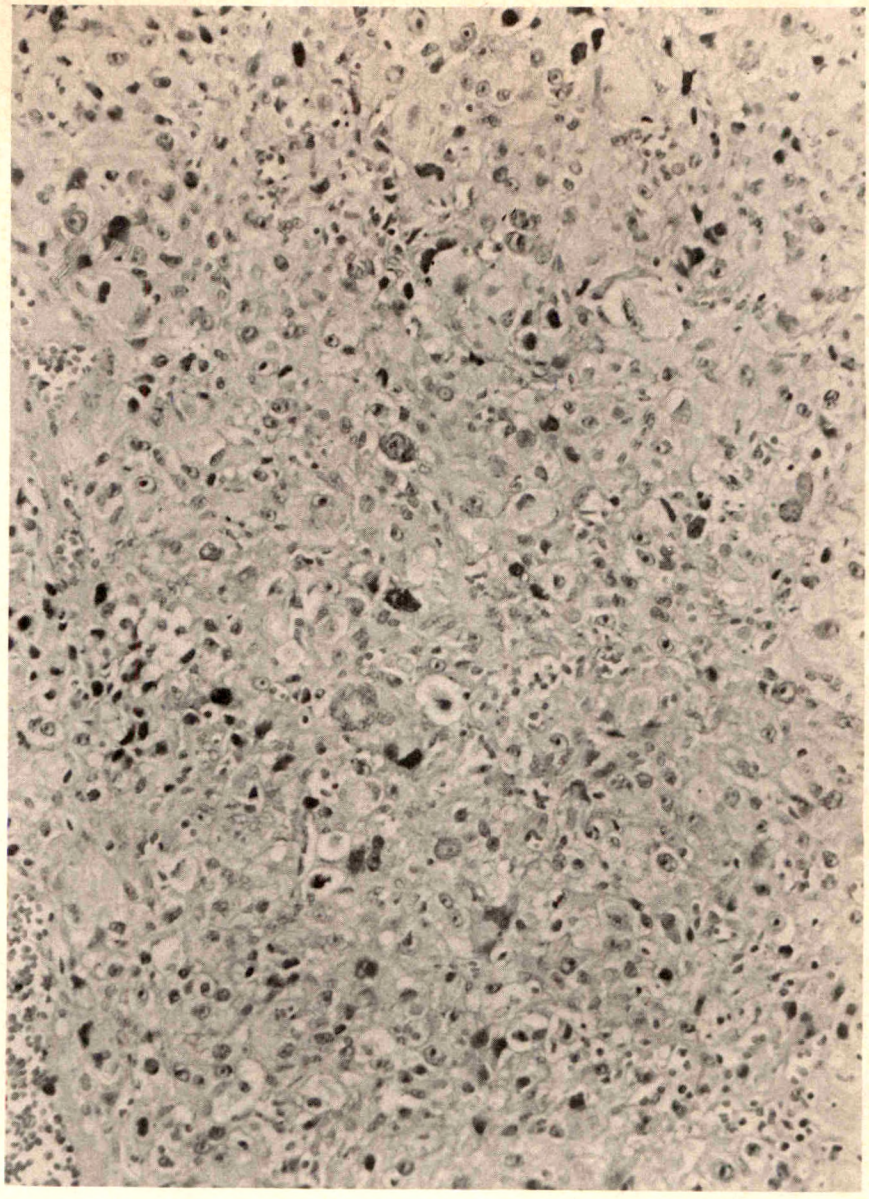


Fig. 2. Case 9. Grade 4 leiomyosarcoma with 2 MF/10 HPF. (Hematoxylin and eosin. ×25.)

one of many reviews of this case. On "step-section" slides made from the same tissue block, no comparable area of mitotic activity could be found in contiguous slides, indicating the extreme focal nature of this activity. Similar study of Case 7 demonstrated several areas with 3 MF/HPF.

As noted earlier, quantitative mitotic activity has been used as the sine qua non of uterine leiomyosarcoma, although the exact number of mitotic figures required to make the diagnosis has varied.[2, 3] Even those who deny that elevated mitotic counts are an absolute prerequisite for diagnosis recognize the strong association between increasing mitotic activity and poor outcome.[4, 8] "Smooth muscle tumors of uncertain malignant potential" is a term that includes tumors which have some characteristics associated with malignancy but an insufficient number of mitoses to justify the diagnosis of sarcoma. No single series contains a large enough number of tumors in this category to justify conclusions regarding their behavior (Table IX).

The data collected from these heterogeneous clinical series are, in many ways, impure (Table IX). For example, among tumors with between 5 and 9 MF/10 HPF, Kempson and Bari's[2] series includes five patients in whom the behavior of the tumor can be evaluated, and four of these patients had extrauterine spread of the disease at the time of diagnosis. All of these patients died. Silverberg's[4] patients likewise all died of leiomyosarcoma, but the stage of the disease is not discernible in this subgroup of his patients. A total of 27 cases has

Table IX. Collected series of smooth muscle neoplasms related to numbers of mitotic figures

Author	Total (No.)		Surviving (No.)		Died (No.)	
	1-4 MF/10 HPF	5-9 MF/10 HPF	1-4 MF/10 HPF	5-9 MF/10 HPF	1-4 MF/10 HPF	5-9 MF/10 HPF
Laberge,[9] 1962	16	3*	15	2*	1	1*
Kempson and Bari,[2] 1970	9	5†	9	0	0	5
Silverberg,[4] 1971	10‡	8‡	9‡	5‡	1‡	3‡
Belgrad and associates,[10] 1975	3	4	3	4	0	0
Hannigan and Gomez, 1978	4§	7	1	5	3	2
Total	42	27	37	16	5	11

*Used 3 to 10 MF/10 HPF.
†Four extended beyond uterus.
‡Stage not stated.
§One extended beyond uterus.

been collected and eleven of the patients (41%) died of uterine sarcoma. Despite the impurity of the data, the conclusion that the diagnosis of leiomyosarcoma can be made with fewer than 10 MF/10 HPF is justified.

Among 42 collected cases with less than 5 MF/10 HPF, five patients (12%) died, three of whom are included in the patients discussed in this paper (Table IX). As stated earlier, one of these three tumors displayed severe anaplasia, and another was spread beyond the confines of the uterus at the time of initial surgery, but the third is a bona fide case of moderately well-differentiated neoplasm with a low mitotic count, confined to the uterus.

The relatively large number of tumors in this series with low mitotic activity possibly may be explained in several ways. Emphasis was placed on the pathologic features in the primary uterine tumor and a metastatic nodule was evaluated in only one case. This may lower the mitotic index by both selecting against tumors with pronounced mitotic activity and excluding from the mitotic count foci of tumor that possibly contain areas of more active cell division. The arbitrary requirement that the mitotic count be determined by figures observed in 30 HPF on two occasions may be too rigorous. Areas of high activity can be diluted by the inclusion of multiple fields in which no activity is noted. An attempt was made to circumvent this difficulty by considering the group of in situ tumors as a separate entity, including in the count only those areas of sarcomatous change and excluding the surrounding benign-appearing myoma. Even large, homogeneous-appearing sarcomas, however, have extreme variations in mitotic activity between two adjacent foci. A more useful mitotic index may be a figure which reflects the highest level of activity observed in any single microscopic field rather than the average of many fields.

Examination of our cases using this index suggests but does not prove a relationship between aggressiveness and mitotic activity. Moreover, the small difference in mitotic figures per single high-power field obtained in tumors confined to the uterus was found only by laborious retrospective examination of tumors whose biologic behavior was already known.

In summary, the extent of the disease at the time of initial diagnosis is of great prognostic significance. Among those tumors confined to the uterus, both histologic grade and mitotic activity are prominent prognostic factors: Worsening atypia or high mitotic counts are associated with a poor outcome. Although the prognosis improves with decreasing mitotic activity, there is no level of mitotic activity below which the diagnosis of uterine leiomyosarcoma can be excluded.

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Further observations on the effect of topical progesterone on vulvar disease

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Follow-up studies have confirmed the beneficial effect of topical progesterone in the treatment of vulvar dystrophy, whether of the atrophic, hypertrophic, or mixed variety, in both postmenopausal and premenarchal women. If pruritus is a major symptom, topical corticosteroids should be alternated with the progesterone preparation in order to obtain maximum results. Topical progesterone was also found to be useful in the treatment of labial agglutination in children.
(AM. J. OBSTET. GYNECOL. 134:565, 1979.)

THE FACT that topical progesterone is effective in the treatment of vulvar dystrophy has been previously reported.[1] In four of the original five patients treated, pruritus was not a prominent symptom. These patients responded promptly to topical progesterone, although intravaginal estrogen was necessary to treat a concomitant senile vaginitis in one instance. The fifth patient, a diabetic woman who had pruritus as a chief complaint, was originally considered to represent treatment failure. Topical corticosteroids were added to control this symptom, and good results were then obtained. Maximal improvement, however, did not occur until the diabetes was brought under strict medical control. Subsequently, six additional cases have been treated.

Method of treatment

1. A complete history is taken and physical examination is done when patients are first seen. Special attention is given to the detection of diabetes and vaginitis of both senile and infectious varieties. If present, these conditions are treated prior to institution of therapy. Laboratory tests therefore include a glucose tolerance test and sodium chloride and potassium hydroxide vaginal smears.

2. A provisional diagnosis must be confirmed by histologic specimen.

3. The patients are given a prescription for 200 mg of progesterone in oil to be mixed in 2 ounces of hydrophilic ointment. They are instructed in the local application of a small amount, twice daily. Once a satisfactory response is achieved, this is decreased to a once-a-day application. After one month on this schedule, this is further decreased to every second day and the results are observed.

4. In the presence of pruritus, an additional preparation for a corticosteroid is given (15 gm of 0.1% Valisone ointment*). In these cases, the progesterone is applied in the morning and the corticosteroid in the evening. With an atrophic variety of vulvar dystrophy, the patients are instructed to discontinue the corticosteriod as soon as the itching subsides.

The patients are seen every two weeks for the first three months and then on a monthly basis. Unusual symptoms or reactions are reportable at any time.

Case report

Mrs. A. L., a 71-year-old woman, had been treated by various physicians during the past several years for primary symptoms of vulvar itching and burining. She had received multiple medications for the treatment of these symptoms, including intravaginal sulfa preparations and Mycolog ointment† externally. When first seen, her symptoms were at their maximum (Fig. 1). On observation, the labia were markedly irritated and had a tissue-paper appearance. Vaginal smears were negative for infection. A glucose tolerance test was normal. A presumptive diagnosis of atrophic vulvar dystrophy was made and confirmed by punch biopsy. Treatment consisted of alternate applications of progesterone and corticosteroids.

Two weeks following the initiation of therapy (Fig. 2),

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*Schering Corporation, Kenilworth, New Jersey.
†E. R. Squibb & Sons, Princeton, New Jersey.

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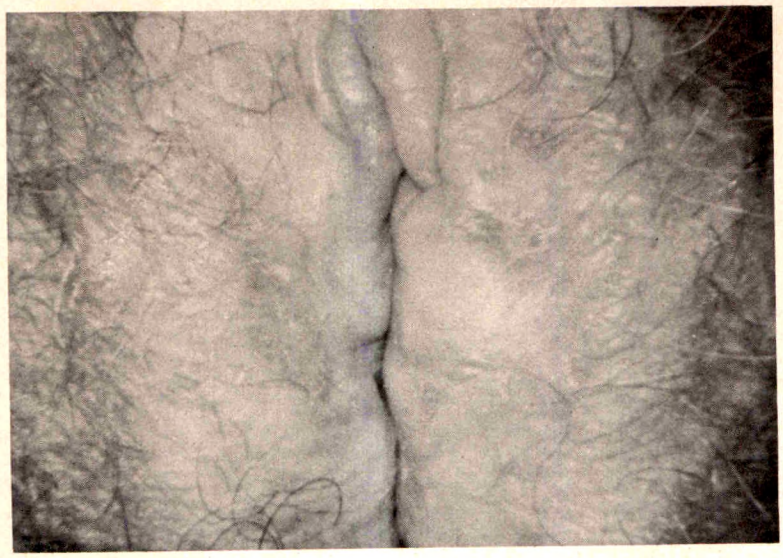


Fig. 1. Appearance at beginning of treatment. Note thinning of the skin.

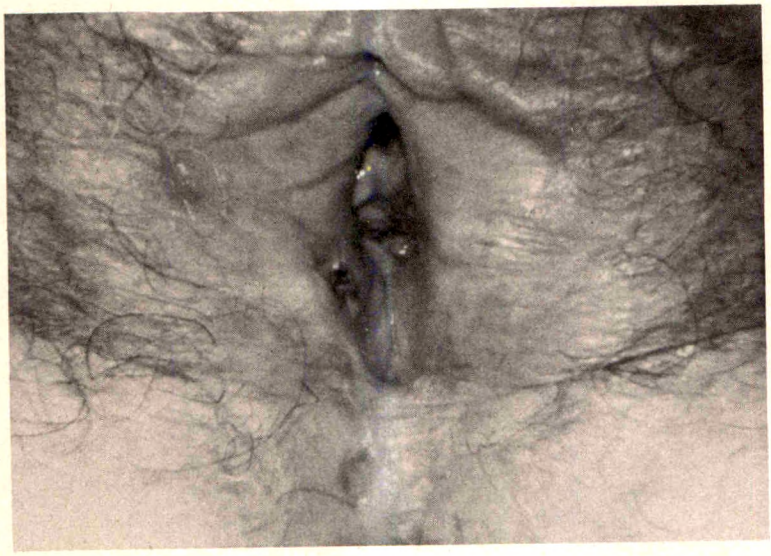


Fig. 2. Two weeks following initiation of therapy. Note biopsy sites at 6 o'clock and 9 o'clock positions. Subjectively the patient is much improved and objectively she is healing.

the patient was much better and was healing. Improvement continued. After 2 months corticosteroids were used only occasionally and after 3 months the progesterone preparation was decreased to every second day.

Results

All six of the new patients responded favorably to therapy. Three of these patients required corticosteriods in addition to progesterone. As noted before, symptoms recurred slowly when treatment was discontinued or tapered off too rapidly. The amount of medication required to maintain remission was found to decrease in proportion to duration of treatment. Interestingly, the first patient treated has been without medication for the past 6 months and subjectively and objectively has had no recurrence. No systemic side effects were noted in any of the patients. One patient noted a localized burning following application of the medication. The vehicle was changed from hydrophilic ointment to oil of petrolatum and was found to be satisfactory. One patient had candida vaginitis which was treated with Monistat cream* prior to initiation of therapy.

*Ortho Pharm. Corp., Raritan, New Jersey.

Treatment of vulvar dystrophy

The question of whether topical progesterone would also be effective in the treatment of vulvar dystrophy in premenarchal patients has also been considered. We have received personal communications from several gynecologists who have successfully treated five cases of the atrophic variety. The response to therapy appears to be slower than in postmenopausal women.

Since topical progesterone appears to have a healing or rejuvenating effect on ectoderm, we decided to use it for the treatment of labial agglutination in children. This condition is usually treated with a combination of manual separation of the labia minora plus application of an estrogenic cream.[3] Some cases takes months for complete separation to occur. Since topical estrogen has no beneficial effect on skin,[2] it is possible that the healing is achieved despite the estrogen content, that is, because of the mechanical separation and the vehicle present in the cream. We used small amounts of the preparation in the treatment of four patients.

Method of treatment. At the time of the first examination, the labia are separated and small amounts of ointment are applied to the area with a cotton swab. The mothers are instructed to repeat this procedure twice a day for 2 weeks and once a day for 2 additional weeks.

A satisfactory response was obtained in all four patients. One of them was an 8-year-old girl who had been resistant to previous therapy, which included estrogen cream. Following 1 month's treatment, labial separation was achieved. No systemic side effects were noted. A slight burning on local application of the ointment was noted in one patient.

Comment

Topical progesterone relieves burning, dryness, and dyspareunia associated with atrophic, hypertrophic, and mixed varieties of vulvar dystrophy. This gives credence to those investigators who claim that these histologic entities are but variants of the same disease process.

Itching, a common symptom, especially of the hypertrophic variety, is not relieved by the topical use of progesterone. A regimen of topical corticosteroids must be alternated with topical progesterone to achieve maximum subjective and objective effect. Previous investigators[2] have shown that topical corticosteroids cause a thinning of tissues which would thereby account for the hastening of the recovery process observed in the hypertrophic variety of vulvar dystrophy. These should be used sparingly in the presence of the atrophic variety.

No systemic side effects were noted in any of our patients. One of the patients complained of localized burning following application of the medication. Oil of petrolatum was substituted for the vehicle and this preparation was found to be satisfactory.

Topical progesterone appears to be effective in the treatment of the atrophic variety of vulvar dystrophy in the premenarche. Topical progesterone also appears to have a healing effect on ectoderm in the vulvar area and is therefore useful in the treatment of labial agglutination.

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Comparison of three different models of the Copper T intrauterine contraceptive device

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A random sequential comparative study of three models of the Copper T intrauterine contraceptive device (IUD) was undertaken in 1,792 women. For 7 months, the TCu 300 and TCu 220C were randomly inserted, and then the TCu 380A and 220C were randomly inserted for the next 12 months. The log-rank method of life-table analysis of event rates was performed at the end of each of the first 3 years of use of each device. The TCu 380A had the lowest pregnancy rate during each year of use, although the difference was not significant. At the end of each of the first 2 years, the TCu 300 was removed significantly less than the TCu 220C and TCu 380A for bleeding and pain. At the end of three years, the rates of removal for bleeding and pain for the TCu 380A and TCu 300 were similar and lower than that for the TCu 220C, but the overall difference was not significant. There were no differences among the devices for any other relevant use-related reasons. The TCu 380A was removed for other medical reasons significantly more frequently than the other devices at the end of 2 and 3 years. Adjusting for parity did not alter the results. The findings of this study suggest that the copper sleeves along the horizontal arms together with copper wire on the vertical arm in the TCu 380A model provide greater protection against intrauterine pregnancy, whereas the copper sleeves along the vertical arm as in the TCu 220C caused increased removals for bleeding and pain. The TCu 380A should be studied in a larger number of patients for a longer period of time to determine its clinical effectiveness. It may become the IUD of choice for all women irrespective of parity. (AM. J. OBSTET. GYNECOL. 134:568, 1979.)

THE COPPER T 200 (TCu 200) with 200 sq mm copper wire wound around the vertical arm of the plastic T-shaped device has had extensive clinical testing and is now widely used throughout the world.[1–3] It has recently been approved by the Food and Drug Administration for use in the United States. Attempts have been made to improve the effectiveness and longevity of the copper intrauterine contraceptive devices (IUDs) by increasing the amount of copper wire along the vertical arm, as in the TCu 300 model, by placing solid copper sleeves on the horizontal arm in combination with either copper wire on the vertical arm, as in the TCu 380A model, or copper sleeves on both the horizontal and vertical arms, as in the TCu 220C model.

A randomized clinical study comparing the TCu 220C and the TCu 300 indicated that there were no significant differences in use-related termination rates between these two devices.[4] As the TCu 380A has one design characteristic in common with both the TCu 300 and the TCu 220C, it was thought to be of interest to compare the performance of these three Copper T IUDs to determine if there was a difference in event rates that might then be related to design of the device.

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Material and methods

Both nulliparous and parous women attending the Family Planning Clinic of Women's Hospital, who were willing to participate in the random assignment and

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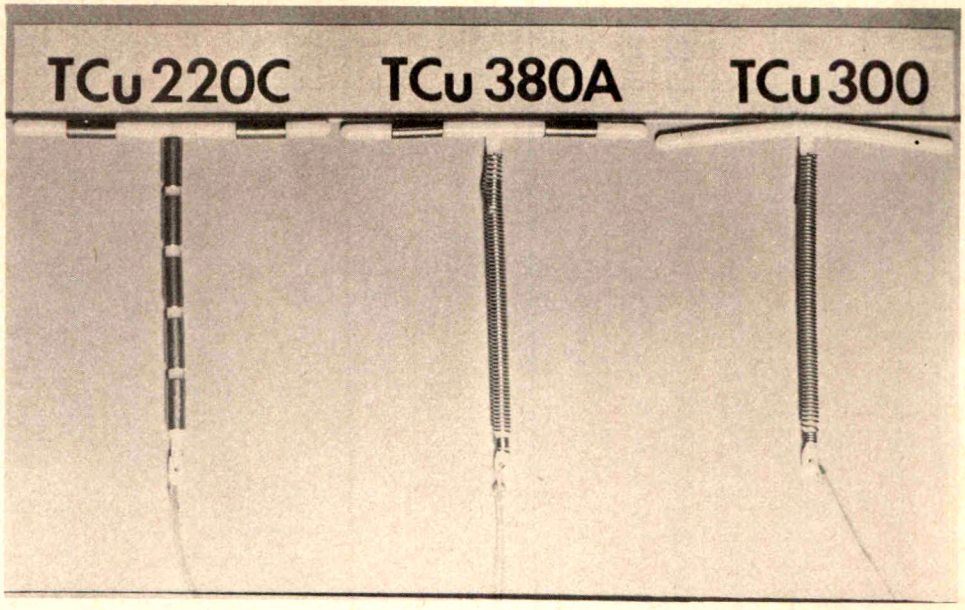


Fig. 1. Configuration and composition of the TCu IUDs used in the study.

follow-up procedures of these three investigational devices, were enrolled in this study.

The enrollment period for this study was from January 2, 1973, to August 13, 1974. A total of 1,792 TCu devices were inserted during this period. The device was chosen according to the last digit of the patient's previously assigned clinic number. All patients with odd numbers had the TCu 220C inserted. From January 2, 1973, to July 31, 1973, all patients with even numbers had the TCu 300 inserted and from August 1, 1973, to August 13, 1974, patients with even numbers had the TCu 380A inserted. Thus, the three devices were not studied in the same time period. The TCu 220C was first compared with the TCu 300 and then with the TCu 380A. A total of 903 women received the TCu 220C while 498 had the TCu 300 and 391 had the TCu 380A inserted. All devices were inserted by Family Planning Clinic staff physicians with the use of a modified loop inserter and push-in technique.[5]

The TCu 300 and the TCu 380A each have 300 sq mm of copper wire wound around the vertical arm. Both the TCu 380A and the TCu 220C have one copper sleeve of approximately 30 sq mm on each horizontal arm. The TCu 220C has five of these sleeves along its vertical arm instead of the copper wire (Fig. 1).

The log-rank method of life-table analysis[6, 7] was employed to generate event rates and to test for differences among the devices at 1, 2, and 3 years of use according to the categories as recommended by Tietze and Lewit[8] with the exception that a subject was considered a loss to follow-up if no contact was made by the time of the scheduled visit. The cut-off date was October 1, 1977, and the analysis was made after December 1, 1977, to ensure that no pregnancies were overlooked.

Results

There were no significant differences in termination rates for the TCu 220C in all use-related and loss–to–follow-up categories in the two groups of women inserted with the TCu 220C in the sequential time periods. They were, therefore, combined for purposes of analysis.

The percentage of nulliparous and parous women having each of the three devices inserted was similar (Table I). The mean age, gravidity, and parity of the parous women were similar for each IUD (Table II). The nulliparous women also had a similar mean age and percent gravidity (Table III).

The cumulative number of termination events in all patients with each type of device after 1, 2, and 3 years of use is shown in Table IV.

The net cumulative probabilities for termination at 1, 2, and 3 years are given in Tables V, VI, and VII, respectively. These tables also contain the χ^2_2 and P value associated with the testing for differences among the devices for each category, as well as woman months at risk.

Pregnancies. The pregnancy rate was lowest for the TCu 380A at each yearly interval after insertion but the differences in pregnancy rates among the devices were not statistically significant.

Of the 33 pregnancies, two were ectopic. Both occurred in the TCu 220C group, 165 and 195 days after

Table I. Device inserted in parous and nulliparous women

	TCu 220C	*TCu 380A*	*TCU 300*
No. inserted	903	391	498
Parous (%)	238 (26%)	99 (25%)	146 (29%)
Nulliparous (%)	665 (74%)	292 (75%)	352 (71%)

Table II. Device inserted in parous women

	TCu 220C	*TCu 380A*	*TCu 300*
No.	238	99	146
Mean age (range)	24.3 (15-45)	26.0 (17-49)	25.1 (15-42)
Mean gravidity (range)	2.0 (1-6)	2.0 (1-6)	2.3 (1-9)
Mean parity (range)	1.6 (1-5)	1.6 (1-4)	1.9 (1-9)

Table III. Device inserted in nulliparous women

	TCu 220C	*TCu 380A*	*TCu 300*
No.	665	292	352
Mean age (range)	22.5 (15-39)	22.7 (14-36)	22.5 (14-40)
Gravid (%)	28	27	30

insertion in a parous and nulliparous patient, respectively.

Expulsion. There were no significant differences for rates of expulsion among the devices in the three yearly intervals after insertion.

Bleeding and pain. The rate of removal for bleeding and pain with the TCu 300 1 and 2 years after insertion was significantly less than the rates for the other two devices. At the end of 3 years, however, the rate of removal for bleeding and pain for the TCu 380A was not significantly different from that of the TCu 300. The removal rates for bleeding and pain for these two devices 3 years after insertion, however, were not significantly lower than the rate for the TCu 220C.

Other medical indications. The TCu 380A had a significantly greater frequency of removal for other medical reasons 2 and 3 years after insertion. Vaginal discharge was the most common other medical reason for discontinuation. Removals for salpingitis or endometritis did not occur significantly more frequently for any IUD at any yearly interval. The average annual rate of removal of any IUD for pelvic infection was 0.6%. There was one patient with an infected endometrioma who had a TCu 300. No tuboovarian abscesses were reported.

There were three non–IUD-related deaths: two in the TCu 220C and one in the TCu 380A group. A subject with lupus erythematosus died of acute respiratory failure, while another subject died of acute myocarditis, and the third subject died of leukemia. The IUD was not causally related to any of these deaths.

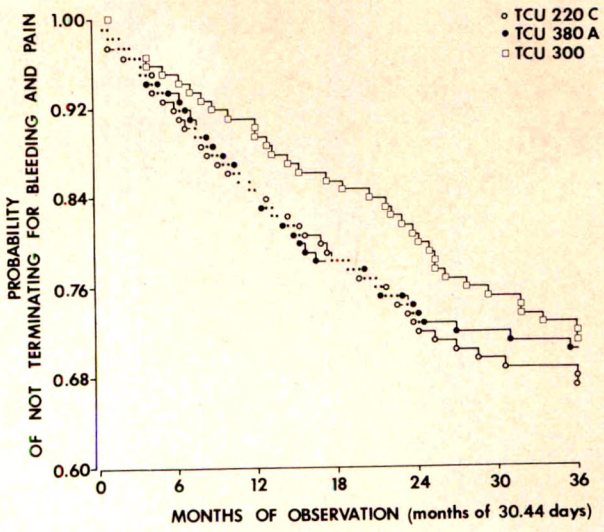


Fig. 2. Probability of not terminating as a result of bleeding and pain as a function of months of observation. Randomly assigned groups of women had the TCu 220C, the TCu 380A, and the TCu 300 inserted. Each vertical drop represents the time at which a patient terminated use of an IUD for bleeding and pain. The dots indicate overlapping of curves.

Planning pregnancy and personal indications. There were no significant differences among the rates of removal in this category among the three IUDs for any yearly time period.

Cumulative relevant terminations: Pregnancy, expulsion, and bleeding and pain. The TCu 300 had the lowest cumulative relevant termination rate at each time interval studied. It was significantly lower than the other devices by 1 and 2 years but not by 3 years after insertion.

Cumulative total terminations. The TCu 300 had the lowest cumulative termination rate for all use-related categories at the first and second yearly time intervals. The differences were not significant at any time intervals.

Loss to follow-up. There were no significant differences in the loss–to–follow-up category at any yearly time intervals.

Parity. Adjusting for parity did not change the results for any of the termination categories.

Comment

The percentage of woman months at risk by device by year was unchanged during the study. The TCu 220C contributed about 50% of the woman months at risk; the TCu 300, about 30%; and the TCu 380A, about 20% in each year of the study. This distribution was expected as a result of the staggered enrollment of

Table IV. Cumulative number of events in all patients using TCu IUDs after 1, 2, and 3 years

	1 yr.			*2 yr.*			*3 yr.*		
	220C	*380A*	*300*	*220C*	*380A*	*300*	*220C*	*380A*	*300*
Number of patients:									
Start of period	903	391	498	587	253	341	384	155	28
End of period	587	243	341	384	155	228	270	86*	130
Termination event:									
Pregnancy	8	2	6	15	3	9	18	3	12
Expulsion	46	17	22	58	25	34	65	32	39
Bleeding and pain	125	56	45	199	84	76	221	88	97
Other medical indications	11	11	11	25	24	20	32	29	24
Planning pregnancy	29	10	16	56	17	32	67	23	44
Personal indications	17	7	12	43	24	20	54	34	34
Loss to follow-up	80	34	44	119	57	74	173	81	111

*There were 100 women at risk at 34.3 months.

Table V. Cumulative net probabilities (p:%) for TCu devices with testing for differences among the devices (χ^2_2, P value) for the various termination categories: After 1 year

Termination event	*220C (%)*	*380A (%)*	*300 (%)*	χ^2_2	*P*
Pregnancy	1.1	0.5	1.5	1.09	0.58
Expulsion	5.7	5.2	4.9	0.58	0.75
Bleeding and pain	15.6	16.3	10.2	8.07	0.02
Other medical indications	1.6	3.5	2.7	4.10	0.13
Planning pregnancy	4.2	3.1	3.9	0.42	0.81
Personal indications	2.3	2.3	2.9	0.44	0.80
Cumulative relevant terminations*	21.3	21.1	15.8	5.99	0.05
Cumulative relevant continuations	78.7	78.9	84.2		
Cumulative total terminations†	27.5	27.9	23.6	2.84	0.24
Cumulative total continuations	72.5	72.1	76.4		
Loss to follow-up	10.2	9.8	10.1	0.03	0.98
Woman months at risk‡	8,905	3,890	5,077		

*Includes pregnancy, expulsion, bleeding and pain.
†Includes all termination events listed above.
‡Calculated by dividing woman days at risk by 30.44 (the average number of days per month).

subjects into the study. Despite these differences in observed experience, the advantage of the log-rank method of life-table analysis allows not only for calculations of termination rates but also for hypothesis testing among these devices in a very accurate manner.

This study demonstrated the value of a long-term examination for trends in event rates since not all short-term differences were maintained at a later time.

In this study, the rate of termination for other medical reasons for the TCu 380A was significantly greater than that for the other two devices at both the 2 and 3 year time intervals after insertion. For all other termination categories, a statistically significant earlier difference was not maintained at subsequent yearly time intervals (e.g., bleeding and pain and cumulative relevant terminations). The rates of removal for bleeding and pain were significantly different in each of the first 2 years; however, the difference among these devices changed. The TCu 300 had a lower rate of removal than both the TCu 220C and TCu 380A for bleeding and pain 1 and 2 years after insertion. By 3 years, both the TCu 300 and TCu 380A had a lower rate of removal than the TCu 220C for bleeding and pain as determined by partitioning of the χ^2,[7] but the overall difference among the three devices was not significant.

In graphic form, the probability of not terminating for a termination category is represented by a survival curve.[6] In this study, the survival curves, as a function of time, move apart for other medical indications and closer together for the other termination categories. In the removal for bleeding and pain category, however, the curve for the TCu 380A moves toward the TCu 300 and away from the TCu 220C curve between the second and third year of use (Fig. 2).

The pregnancy rate was not significantly different for any of the devices although there appeared to be a temporal downward trend favoring the TCu 380A. This suggests that if the sample size were larger the lower pregnancy rate associated with the TCu 380A may have been significantly lower than for the other

Table VI. Cumulative net probabilities (p:%) for TCu devices with testing for differences among the devices (χ^2_2, P value) for the various termination categories: After 2 years

Termination event	*220C (%)*	*380A (%)*	*300 (%)*	χ^2_2	*P*
Pregnancy	2.6	1.0	2.6	1.70	0.43
Expulsion	8.1	8.7	8.9	0.02	0.99
Bleeding and pain	27.6	27.1	19.7	9.74	0.01
Other medical indications	4.4	9.6	5.9	8.52	0.01
Planning pregnancy	9.3	6.5	9.2	1.68	0.43
Personal indications	7.3	10.3	5.6	2.64	0.27
Cumulative relevant terminations*	35.2	34.1	28.7	6.10	0.05
Cumulative relevant continuations	64.8	65.9	71.3		
Cumulative total terminations†	48.2	50.0	42.5	5.14	0.08
Cumulative total continuations	51.8	50.0	57.5		
Loss to follow-up	17.1	19.9	18.8	0.58	0.75
Woman months at risk‡	14,758	6,337	8,448		

*Includes pregnancy, expulsion, and bleeding and pain.

†Includes all termination events listed above.

‡Calculated by dividing woman days at risk by 30.44 (the average number of days per month).

Table VII. Cumulative net probabilities (p:%) for TCu devices with testing for differences among the devices (χ^2_2, P value) for the various termination categories: After 3 years

Termination event	*220C (%)*	*380A (%)*	*300 (%)*	χ^2_2	*P*
Pregnancy	3.4	1.0	4.3	2.99	0.22
Expulsion	10.0	13.2	11.5	0.52	0.77
Bleeding and pain	32.3	29.7	28.5	4.60	0.10
Other medical indications	6.4	13.3	7.8	9.80	0.01
Planning pregnancy	12.4	11.3	15.4	1.69	0.43
Personal indications	10.1	18.6	12.7	4.89	0.09
Cumulative relevant terminations*	41.2	39.5	39.5	2.39	0.30
Cumulative relevant continuations	58.8	60.5	60.5		
Cumulative total terminations†	57.0	62.2	58.9	2.17	0.34
Cumulative total continuations	43.0	37.8	41.1		
Loss to follow-up	30.3	34.6	35.2	1.86	0.40
Woman months at risk‡	18,669	7,742	10,561		

*Includes pregnancy, expulsion, and bleeding and pain.

†Includes all termination events listed above.

‡Calculated by dividing woman days at risk by 30.44 (the average number of days per month).

two devices. This corroborates previous reports for various TCu devices studied for shorter intervals of use.[4, 9] Only three pregnancies occurred among women with the TCu 380A. One of these followed on unnoticed expulsion. None of the pregnancies occurred after 2 years of use. Since prevention of pregnancy is the main objective of a contraceptive method, this superior performance of the TCu 380A, although not statistically significant in this study, warrants further long-term large-scale evaluation.

Since only two ectopic pregnancies occurred in this study, no conclusions regarding type of device, duration of use, or parity can be made.

Removals for bleeding and pain accounted for the greatest numbers of removals in the use-related categories similar to previous studies.[10] One year following insertion, a significant difference in the removal rates for bleeding and pain was found in this study, in contrast to the lack of a significant difference previously reported with the same data analyzed by a different method.[4] This difference in significance is attributable to the following two factors related to the log-rank method of life-table analysis. First, in this type of analysis, patients not seen after insertion contributed no woman months of use in the data base. Second, the χ^2 test statistic employed is more sensitive than the overlapping confidence interval approach, which is based on a less exact calculation of standard error. A detailed comparison of log-rank and Tietze methods of life-table analysis has recently been reported.[6]

The greater number of removals for other medical reasons for the TCu 380A was investigated further

The charts of all patients who had the IUD removed for this category were examined to determine whether any bias in the distribution of patients might have contributed to the poorer experience in this category with the TCu 380A in comparison with the TCu 220C and TCu 300. None was found. This difference apparently occurred by chance since removal for other medical reasons is most likely not related to the type of IUD.

Although some studies have suggested that IUD usage increases the risk of developing pelvic inflammatory disease (PID),[11, 12] others have not.[10, 13] None has studied a cohort of women with appropriate control subjects using no method of contraception by life-table analysis. Since the relation of the IUD to development of PID and salpingitis has not been confirmed, the category of other medical removals for salpingitis or endometritis was not considered a relevant use-related risk for termination of IUD usage in this study.

Removals for planning pregnancy or other personal reasons in some instances were the next most common reasons for terminating use of the IUD. Removals for these categories were higher than in other reports.[9, 10] The cumulative total continuation rate, therefore, was lower for similar time periods.[9, 10] The cumulative relevant continuation rate, which reflects the strictly use-related termination categories (pregnancy, expulsion, and bleeding and pain), is a better means to compare different IUDs.

From the point of view of family planning programs, the success of a device is measured in terms of overall continuation rates, which are similar for the three devices described here. However, from the woman's point of view, unplanned pregnancy is far more important than the inconvenience of expulsion or removal for pain, bleeding, or other medical reasons. If a woman conceives with an IUD in place, she is forced into a decision which is based on documented risks. These include the risks of terminating the pregnancy,[14] the chance of inducing a spontaneous abortion if the device is removed,[15] and, if the device is not or cannot be removed, the risk of spontaneous abortion, infection, or premature delivery.[15] The copper sleeves were placed on the horizontal arms in an attempt to provide a copper-bearing surface in the fundal region and thus reduce the chance of an accidental pregnancy in the event of downward displacement. The TCu 380A device had the lowest pregnancy rates at each annual interval studied while the TCu 220C device had rates similar to those of the TCu 300 device. Thus, one device with horizontal sleeves had a reduced pregnancy rate and the other did not. Although the pregnancy rate associated with the TCu 380A did not differ significantly from that of the other devices, the low rate observed with this device suggests that additional study would demonstrate it to be more effective than the other devices. The pregnancy rate with the TCu 380A is comparable to that experienced by oral contraceptive users.[16]

Since the horizontal arms containing copper sleeves are less flexible than those without sleeves, they could produce a downward displacement of the device with uterine contractions. The resulting downward movement of these devices may cause increased bleeding and pain. The TCu 220C had the highest removals for bleeding and pain after three years while the TCu 380A and TCu 300 were not different. The structural difference between the TCu 380A and the TCu 220C device is that the former has wire while the latter has copper sleeves on the vertical arm. Perhaps the vertical copper sleeves of the TCu 220C, because of their rigidity, cause increased pain and the uterus responds with increased contractions which produce a further displacement into the lower uterine segment. This could account for the increased pregnancy rate and rate of removals for bleeding and pain of the TCu 220C.

Therefore, the hybrid design of the TCu 380A, which combines sleeves on the horizontal arms and flexible wire on the vertical arm, would appear to incorporate the best features of both the TCu 220C and the TCu 300 in addition to providing the greatest surface area of copper (380 sq mm). It should be studied in larger numbers of patients for a longer period of time to determine its actual clinical effectiveness. If such studies confirm that the TCu 380A, with a predictable lifespan of about 8 years, has the low pregnancy and removal rates found in this study, it may become the IUD of choice for both nulliparous and parous women.

This study was undertaken as part of the Contraceptive Development Program of the International Committee for Contraceptive Research of the Population Council, New York, New York. The technical assistance of Marie Fielding is acknowledged.

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Naproxen sodium in uterine pain following intrauterine contraceptive device insertion

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In a double-blind parallel trial, repeated doses of naproxen sodium (550 mg initially, followed by 275 mg every 6 hours as needed) and placebo were administered to a group of intrauterine contraceptive device (IUD) users in whom dysmenorrhea and premenstrual uterine pain developed or increased following the insertion of the IUD. Seventeen subjects were treated with naproxen sodium and 16 received placebo. The study covered three episodes of uterine pain and/or cramping. Efficacy of pain relief was judged by: (1) the overall relief which the patients experienced during the treatment and (2) the changes in the pain intensity (measured on a 6 point scale). By both these criteria, naproxen sodium was statistically significantly superior to placebo ($p = 0.02$); consequently, naproxen sodium appears to offer a new treatment modality for pain associated with IUD usage. (AM. J. OBSTET. GYNECOL. 134:575, 1979.)

IN 1974, MASSEY and associates[1] reported that treatment wth a prostaglandin synthetase inhibitor (naproxen*) significantly reduced pain and discomfort following intrauterine contraceptive device (IUD) insertion. We have previously tested the analgesic properties of naproxen sodium,* an analogue of naproxen, in dysmenorrhea[2] and noted beneficial effects of this treatment for a number of women practicing intrauterine contraception. This prompted us to investigate the effects of naproxen sodium in a select population of IUD users in whom uterine cramping developed or increased after they had been fitted with IUDs.

Material and methods

The study was a double-blind, randomized, parallel trial in a group of IUD users. The effects of repeated doses of naproxen sodium were compared with those of placebo during episodes of uterine pain.

Patients. Two groups of women participated in the study, namely, those who after insertion of an IUD started to experience uterine pain and those whose previously experienced menstrual pain increased after IUD insertion. A full medical and menstrual history was obtained; particular attention was paid to the temporal relationship of the uterine pain to the IUD insertion and to the onset of menstrual bleeding. Complete physical and pelvic examinations were conducted, supplemented by peritoneoscopy, if indicated, to exclude obvious pelvic disease (inflammation, myomas, endometriosis, ect.). Women with major cyclic irregularities were excluded from the trial.

Thirty-five patients met the admission criteria and were randomly and sequentially assigned to either naproxen sodium or placebo treatment. The double-blind design of the study was explained to the patients, who were likewise told of possible adverse reactions to the active compound. Signed informed consent forms were obtained from all participants in the study.

Medication schedule. Each patient was given a supply of tablets containing either naproxen sodium (275 mg) or placebo (lactose) and was instructed to take two tablets at the first sign of menstrual distress and to continue to take one tablet every 6 hours as needed during the period of uterine pain. In the event that the test medication was not effective, patients were allowed to take the next dose sooner or to resort to a supplemental conventional analgesic, provided a record was kept of

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**Naproxen (Naprosyn) and naproxen sodium (Anaprox) are generic names for (+)2-(6-methoxy-2-naphthyl) propionic acid and its sodium salt.*

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Table I. Relation of dysmenorrhea to IUD insertion

Dysmenorrhea	Before IUD insertion (No. of patients)		After IUD insertion (No. of patients)	
	Naproxen sodium	Placebo	Naproxen sodium	Placebo
Incidence:				
None	5	3	0	0
Occasional	6	3	0	0
Each cycle	6	9	17	15*
Intensity:				
Very severe	0	0	1	4
Severe	1	3	10	9
Moderate	4	8	6	3
Mild	7	2	0	0
None	5	3	0	0
Total	17	16	17	16

*One patient was not included as she took placebo for several days prior to the first menses after IUD insertion and discontinued the placebo on the first day of bleeding because of no relief.

Table II. Number of patients who experienced excellent or good relief during treatment

Good or excellent relief experienced	No. of patients	
	Naproxen sodium	Placebo
In all three dysmenorrheic episodes	7	2
In two dysmenorrheic episodes	3	1
In one dysmenorrheic episode	4	1
In none of the dysmenorrheic episodes	3	12
Total	17	16

p Value = 0.003 (two-sided Mann-Whitney U test for group differences).

the dose concerned and the time it was taken.

Assessment of the drug effect. The patients were instructed to keep detailed records on which they noted the baseline pain intensity (i.e., pain intensity prior to the drug intake), the study drug intake, the relief achieved, and the necessity (if any) to take supplemental analgesic medication. From these entries, the effectiveness of the study drug was assessed by the overall rating of relief and by computing the "daily pain relief scores" (see details in the "Results" section).

Results

Demography. Of the 35 subjects originally enrolled, two left the trial for personal reasons. Data were analyzed for the remaining 33 subjects, 17 treated with naproxen sodium and 16 given placebo. Twenty-seven subjects were treated during three menstrual periods, 15 with naproxen sodium and 12 with placebo. Six subjects were treated for one or two dysmenorrheic episodes only; they either did not experience sufficient relief of symptoms (two of the naproxen sodium group and one of the placebo group) or had no need for further treatment (no dysmenorrhea, two patients; IUD removal, one patient; all three were in the placebo group).

The patients of the two treatment groups were comparable in ethnic background, age (means were 26.4 years, for the naproxen sodium group and 24.7 years for the placebo group), obstetric history, and individual history of dysmenorrhea.

The incidence and degree of dysmenorrhea before and after IUD insertion are given in Table I. The extent to which the pain increased in frequency and intensity after IUD insertion is obvious. All patients, except one, had been using analgesics for uterine pain before entering the study, but only three with noticeable effect.

Baseline pain intensity (i.e., pain experienced before the initiation of treatment) was scored on a 4 point scale: (1) very severe, (2) severe, (3) moderate, and (4) mild. Only patients who completed all three treatment courses were included in this analysis. For each treatment course, the scores obtained on individual days of dysmenorrhea were averaged and summed over the three treatment courses (the lower values represented higher pain intensities; see Fig. 2). It was interesting to observe that, despite the random allocation of patients to the two study medications, less pain was experienced by placebo-treated patients prior to the intake of the study drug (mean value of the sum of the baseline pain intensity scores, 8.57 ± 0.42 [SE]) than by the patients who were treated with naproxen sodium (mean value of the sum of the baseline pain intensity scores, 7.68 ± 0.26 [SE]; p = 0.021).

The overall rating of relief. For this evaluation, all 33 patients participating in the study were taken into account. After each dysmenorrheic episode, the patients assessed the effects of the study drug over the entire treatment course by scoring the experienced relief on a 6 point scale: 6, excellent; 5, good; 4, moderate; 3, fair; 2, poor; and 1, no relief experienced.

The overall relief scores were summed over all three treatment courses, and means were calculated for each treatment group, higher numbers indicating more pronounced relief. This type of evaluation was conducted irrespective of whether or not the patient had recourse to supplemental analgesia and regardless of the baseline pain intensity.

The results are summarized in Fig. 1. For the naproxen sodium group, the mean sum of the overall re-

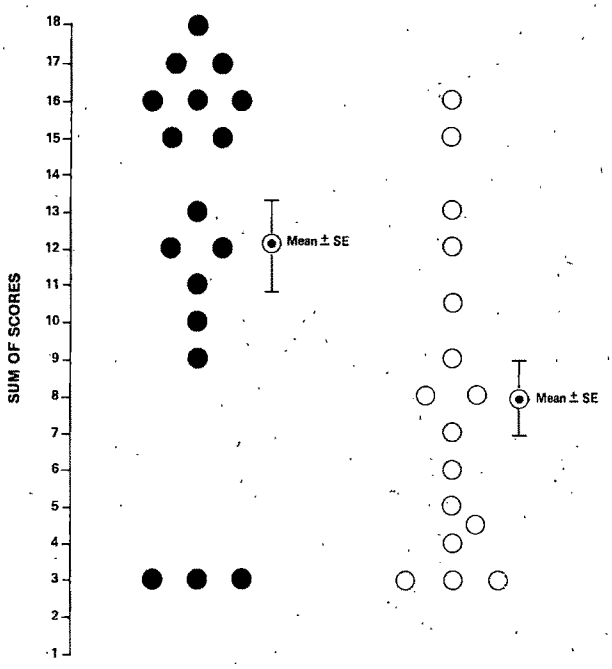


Fig. 1. Overall rating of pain relief. Sum of overall rating scores in three dysmenorrheic episodes for individual patients. • = naproxen sodium; o = placebo. The higher scores indicate a more pronounced effect of the study drug. The highest sum of scores a patient could acquire was 18; the lowest, 3. See details in text. p Value for difference between groups = 0.021.

lief scores was 12 ± 1.2; for the placebo group, 7.9 ± 1.1. The degree of relief afforded by naproxen sodium was statistically significantly higher by comparison with that associated with placebo administration (p = 0.02, two-sided Mann-Whitney U test). Table II shows that more patients experienced "excellent" or "good" relief in the naproxen sodium group than in the placebo group, with high statistical significance (p = 0.003).

Daily pain relief scores. Only patients who had completed all three treatment courses were analyzed (15 of the naproxen sodium treatment group and 12 of the placebo group). The relief achieved daily was graded as: 6, excellent; 5, moderate; 4, mild; 3, no relief; 2, pain worse; and 1, additional analgesia required. The ratings acquired on individual days of dysmenorrheic episodes were summed and average relief scores were calculated. For each patient, the relief scores were totaled over all three treatment courses. The highest sum of scores a patient could acquire was 18; the lowest, 3. For the group treated with naproxen sodium, the mean of all relief scores was 13.9 ± 0.8 (SE); for the placebo group, 10.8 ± 1.2 (SE) (Fig. 2).

In the statistical analysis, the baseline pain intensity was used as a covariable for each patient and the relief

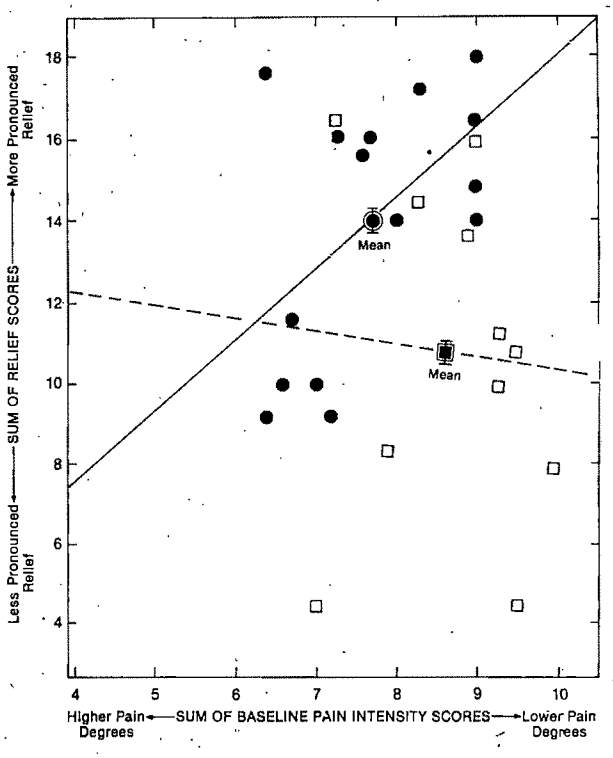


Fig. 2. Baseline pain intensity and pain relief achieved by treatment. Statistical analysis: The "baseline pain intensity score" was used as a covariable; the "relief score" served as the corresponding dependent variable. Baseline pain intensity scores: naproxen sodium group, 7.7 ± 0.26 (mean ± SE); placebo group, 8.6 ± 0.42 (mean ± SE); p = 0.021. Daily relief scores: naproxen sodium group, 13.9 ± 0.82 (mean ± SE); placebo group, 10.8 ± 1.15 (mean ± SE); p = 0.026. The slope of the regression line for the naproxen sodium patients demonstrates the dependence of the pain relief on the baseline pain intensity: Patients with lesser pain degrees at the treatment start experienced more pronounced pain relief. No such correlation is evident in the placebo patients (details in text). • = Naproxen sodium; □ = placebo. —— = Regression line for naproxen sodium patients; ---- = regression line for placebo patients.

scores, as the corresponding dependent variable. A one-way analysis of covariance was computed.[3] The difference in the rating of relief between the two groups was statistically significant in favor of naproxen sodium (p = 0.026).

Fig. 2 displays graphically the relationship between the baseline pain intensity and the relief achieved by the treatment. Each patient's relief score is plotted (on the vertical axis) against the baseline pain intensity (on the horizontal axis). The graph shows that the naproxen sodium–treated patients compared with the placebo patients experienced significantly more pain at the initiation of treatment. Despite that, the relief scores of the naproxen sodium patients were significantly higher than those of the placebo patients.

By fitting regression lines to the points of the two treatment groups, one can observe that the relationship between the baseline pain intensity and the achieved relief is different in the two treatment groups. For the naproxen sodium group, the slope of the regression line indicates that patients with lesser degrees of baseline pain intensity achieved higher pain relief scores than those with higher pain degrees at initiation of the treatment. This corresponds to the clinical impression that patients who started the treatment with the earliest symptoms of dysmenorrhea benefited the most from the treatment. No such correlation could be observed in the placebo patients. The nearly flat regression line demonstrates that the relief (or lack of it) was independent of the baseline pain intensity.

Need for additional medication. Although more patients in the placebo group needed additional analgesics (five during all three treatment courses versus two of the naproxen sodium group), the difference was not statistically significant.

Comment

Naproxen sodium is clearly superior to placebo in alleviating uterine cramping pains caused or aggravated by IUD insertion, and consequently may prove to be a useful drug for this type of condition.

The mechanism of pain relief is probably similar to that through which naproxen sodium is efficacious in primary dysmenorrhea.[2, 5, 6] Hillier and Kasonde[4] demonstrated elevated endometrial prostaglandin E concentrations 1 to 5 months after IUD insertion as compared with values obtained before IUD placement. If this raised prostaglandin concentration indeed contributes to the genesis and augmentation of dysmenorrhea in women practicing intrauterine contraception, then the use of a prostaglandin synthetase inhibitor seems logical as a means of counteracting that pain.

We wish to express our appreciation to Mrs. Carol Janecka, R.N., for coodination of the trial and to Alister Brass, M.D., for editorial assistance.

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CURRENT INVESTIGATION

This section offers prompt first announcement of new observations or discoveries. Articles should be limited to 1,500 words and six references. Illustrations or additional references require a proportionate reduction in total words.

Vasoactive intestinal polypeptide in tissues of the human female reproductive tract

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Vasoactive intestinal peptide (VIP) is a known potent hypotensive and vasodilatory agent. Studies were performed to determine the possible role of VIP in the human menstrual cycle in 44 patients in the reproductive age group, some of whom were using oral contraceptives, three pregnant patients, and four postmenopausal patients. No significant relationship between VIP and menstrual cycle phase was found. (AM. J. OBSTET. GYNECOL. 134:579, 1979.)

VASOACTIVE INTESTINAL PEPTIDE (VIP), a known potent hypotensive and vasodilatory agent with an amino acid sequence related to that of secretin, glucagon, and gastric inhibitory peptide (GIP), has been found by immunocytochemical studies in nerves intimately associated with vessels and smooth muscle of the female genitourinary tracts of pigs, cats, rats, and mice.[1] Most of the VIP-containing nerves were shown to occur in the smooth muscle of the genitourinary organs. However, numerous VIP-containing nerves were also found in the endometrium in a tortuous fashion, suggesting innervation of coiled arteries. Thus, evidence is accumulating that VIP may represent a peptide neurotransmitter which may affect smooth muscle contractility and blood flow.[1]

In order to explore the possible role of VIP in the human menstrual cycle, the levels of VIP were determined by radioimmunoassay in endometrial, cervical, and decidual tissues from women of various ages and phases of the menstrual cycle. The study groups consisted of 44 patients in the reproductive age group with or without the use of oral contraceptives, three pregnant patients, and four postmenopausal patients. None of the women were receiving hormonal treatment other than oral contraceptives. Endometrial tissue samples were obtained under direct visualization at the

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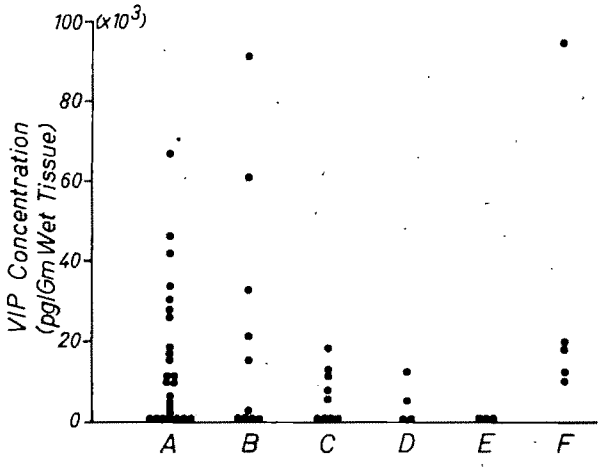


Fig. 1. Distribution of VIP in different tissues and phases of menstrual cycle. *A:* Proliferative endometrium; *B:* secretory endometrium; *C:* endometrium, oral contraceptive users; *D:* endometrium, postmenopausal; *E:* decidua; *F:* cervix.

time of cesarean section for term pregnancy or by dilatation and curettage before hysterectomy or elective sterilization. Cervical tissue was obtained in five patients by punch biopsy. All samples were obtained following general anesthesia and prior to any uterine manipulation. The tissue was frozen immediately on dry ice or in liquid nitrogen and stored at −20° C until the time of analysis. Portions of tissue samples were sent to the Pathology Laboratory for histologic dating of the menstrual phase.

The tissue was weighed to obtain a wet weight before extraction by a modification of the acid-alcohol method previously reported.[2] The tissue was homogenized in 2 to 4 ml of an acid-alcohol solution, refrigerated for 24 hours, and then centrifuged in a cold centrifuge at 2,000 rpm for 30 minutes. The supernatant was decanted, flash evaporated, and reconstituted in 0.05N acetic acid. Aliquots of several dilutions were assayed in duplicate for VIP assay. All determinations were expressed as picograms of VIP per gram wet tissue. The coefficients of variation of intra-assay and interassay reproducibility were 5% and 18%, respectively. The dilution of the human extract paralleled the standard curve for porcine VIP in all assays. Recovery rate of added known amounts of porcine VIP from tissue extract was 80%. A total of 56 tissue samples were assayed. The samples were divided into six different groups based on the source of the tissue, the phase of the menstrual cycle as determined by tissue study, and oral contraceptive usage (Fig. 1).

The present study demonstrated a VIP-like substance to be present in the endometrium and cervix of the woman. The six groups were compared statistically using Student's t test. No significant difference in the VIP levels of endometrial tissues from different phases of the menstrual cycle was found. Measurable amounts of VIP were found in postmenopausal tissues, cervical tissues, and endometrial tissues of those using oral contraceptives. Finally, no measurable levels of VIP were found in decidual tissues of term pregnancies.

In contrast to the known relationship between prostaglandin levels in endometrial tissue and the phases of the menstrual cycle, no such significant relationship could be found for VIP. Large variations of VIP concentration were found in all tissues studied, possibly suggesting a problem in sampling technique or inherent variation among individuals. Furthermore, of the 56 tissue samples, only 14 were from women who were admitted for elective sterilization and who had normal menstrual cycles with no apparent uterine disease. Further evaluation of a large number of women who are menstruating normally may show a direct relationship between the phase of the menstrual cycle and VIP concentrations in endometrial tissue. This may suggest a role for VIP in the regulation of the menstrual cycle.

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Thyrotropin-releasing hormone and thyroid hormones in amniotic fluid

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Immunoassayable TRH (iTRH) was measured in 50 amniotic fluid specimens with a mean concentration of 207 ± 26 (SE) pg/ml. This iTRH demonstrates parallelism with the standard curve for synthetic TRH. With increasing gestational age there is an increase in iTRH levels in amniotic fluid with a decrease in 3,3',5'-triiodothyronine levels (rT_3), while thyroxine levels (T_4) remain unaltered. Preliminary data suggest that iTRH levels in amniotic fluid that are less than 150 pg/ml after 32 weeks of gestation may correlate well with low Apgar scores at birth. There was no correlation of rT_3 or T_4 amniotic fluid levels with the Apgar scores. (AM. J. OBSTET. GYNECOL. 134:581, 1979.)

THYROTROPIN-RELEASING HORMONE (TRH) has been shown not only to be present in the hypothalamus and pituitary but also to be distributed throughout the rest of the brain,[1] retina,[2] gastrointestinal tract,[3] and adrenals.[4] It has been suggested that TRH is a neurotransmitter that has been co-opted by the pituitary to provide a tonic stimulus for TSH release.[1, 3] Recently it has been shown that TRH is present in the placenta and that the placenta is capable of manufacturing TRH from its constituent amino acids in vitro.[5, 16] Thyroxine (T_4) and 3,3',5'-triiodothyronine (rT_3) have been demonstrated in amniotic fluid, whereas triiodothyronine and TSH are not present in detectable amounts.[6] For these reasons we looked for the presence of immunoreactive TRH (iTRH) in human amniotic fluid and have attempted to determine if iTRH can be correlated with Apgar scores at birth.

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Supported by funds from the Medical Research Service of the Veterans Administration and by National Institutes of Health Grant HD-7181.

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Methods

Source of specimens. About 10 ml of amniotic fluid was obtained at various stages of pregnancy. Amniocentesis was performed by transabdominal puncture on 50 occasions in 32 women with pregnancies of 25 to 40 weeks for diagnostic purposes. None of the specimens were visibly contaminated with blood or its products. The results of various tests were correlated with the patients' clinical records. For the purposes of this study we have used an Apgar score of less than 7 at 1 minute or 5 minutes as an index of neonatal distress.

Assays. A total of 2.5 ml of amniotic fluid was extracted in 5 ml of methanol and the supernatant was evaporated to dryness in a water bath at 70° C under a stream of air. The dried extracts were taken up in 0.25 ml of phosphate-buffered saline (0.15M sodium chloride and 0.01M sodium phosphate, pH 7.5) and assayed in duplicate for TRH by radioimmunoassay as described by Bassiri and Utiger.[7] Antiserum to TRH was supplied by Dr. Robert D. Utiger, University of Pennyslvania School of Medicine.

For thyroid hormone assays, 1 ml of amniotic fluid was diluted in 2 ml 95% ethanol. The supernatant was removed and evaporated to dryness in a water bath at 37° C under a stream of air and reconstituted in 1 ml of buffer containing 0.25% bovine serum albumin, 0.02% sodium azide, and 0.0075M barbital at pH 8.6. Aliquots

Table I. Relationship of amniotic fluid iTRH levels to Apgar scores

Apgar score	*TRH (pg/ml)*	*TRH <150 pg/ml (No. of samples)*	*TRH >150 pg/ml (No. of samples)*
1 Minute Apgar score:			
<7	96 = 14	8	1
>7	315 = 73*	4	9
5 Minute Apgar score:			
<7	106 = 17	6	1
>7	290 = 55†	5	10

*p <0.01.
†p <0.05.

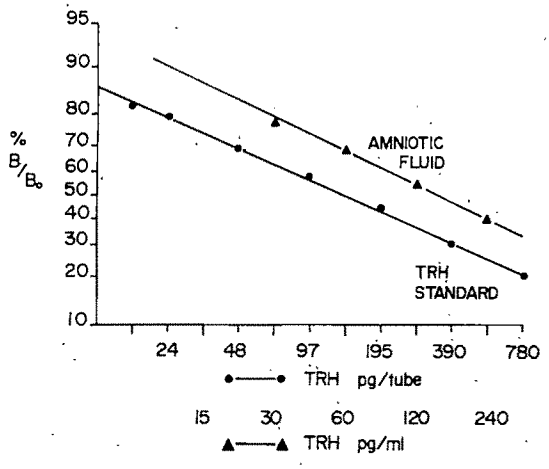


Fig. 1. Demonstration of parallelism of iTRH in amniotic fluid (●——●) with the TRH standard curve (▲——▲) in the TRH radioimmunoassay.

were assayed in duplicate for T_4,[8] and rT_3 was measured with a radioimmunoassay kit from Serono Laboratories, Boston, Massachusetts.[9] The lecithin/sphingomyelin (L/S) ratio was measured as described by Gluck and associates.[10]

Results

We found iTRH in 50 amniotic fluid specimens with a mean concentration of 207 ± 26 (SE) pg/ml. This iTRH demonstrated parallelism with the standard curve of synthetic TRH (Fig. 1). Amniotic fluid, unlike serum, did not degrade synthetic TRH (Fig. 2). Incubation of 0.1 ml amniotic fluid for 2 hours with 0.2 ml human serum resulted in the loss of all immunoassayable TRH. With increasing gestational age (determined from maturity of infant at delivery), iTRH levels in amniotic fluid increase, rT_3 levels decrease, and T_4 levels are unaltered. The amniotic fluid iTRH levels for patients who were subsequently delivered of infants who had 1 minute Apgar scores greater than 7 are given in Fig. 3. Amniotic fluid levels were significantly increased from specimens obtained after 32 weeks (308 ± 5 pg/ml) compared to before 32 weeks (169 ± 31, $p < 0.025$). In amniotic fluid from 23 pregnancies more advanced than 32 weeks, low iTRH levels were more common in those who subsequently had babies with 1 and 5 minute Apgar scores of less than 7 (Table I). Similarly, mean iTRH levels were lower in patients with 1 minute Apgar scores less than 7 ($p < 0.01$) and 5 minute Apgar scores less than 7 ($p < 0.05$). In two normal subjects observed serially during pregnancy there was a rise in amniotic fluid iTRH levels when gestation reached 34 and 35 weeks, respectively. In three subjects with subsequent 1 minute Apgar scores less than 7, there was a rise and then a marked fall in iTRH levels (Fig. 4); these subjects had 5 minute Apgar scores of 7, 8, and 9.

There was no correlation of amniotic fluid iTRH with L/S ratio or T_4 and rT_3 concentrations. T_4 levels in amniotic fluid did not correlate with the L/S ratio or rT_3 levels. There was a significant negative correlation of rT_3 with the L/S ratio ($r = -0.53$, $p < 0.01$). There was no obvious correlation of amniotic fluid rT_3 or T_4 levels with subsequent Apgar scores. In five patients with Rh isoimmune disease, with severely affected fetuses, the rT_3 concentrations were not different from the control values.

Comment

There are many substances of maternal and fetal origin in amniotic fluid. Some of these substances (e.g., cortisol and palmitic acid) vary in concentration with advancing gestational age and most probably reflect the alteration of physiologic conditions leading to delivery.[11, 12] There are, however, no well-documented biochemical criteria either of maturation of the fetal nervous system or of antepartum fetal distress, with the exception of the amniotic fluid bilirubin concentration in cases of isoimmunization. Recently, a preliminary study has suggested that immunoassayable β-endorphin levels in amniotic fluid may be elevated in cases of fetal distress.[13] We have now shown that immunoassayable levels of another neurotransmitter, TRH, are measurable in amniotic fluid and that a fall in

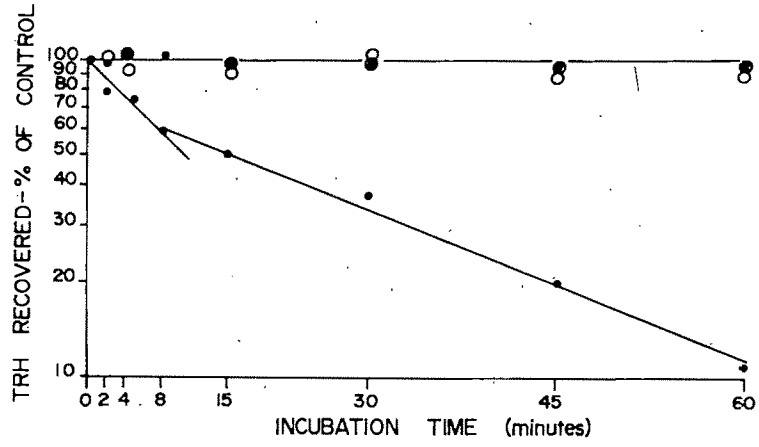


Fig. 2. Failure of amniotic fluid (8——8) to degrade 15 ng/ml synthetic TRH compared to normal degradation of TRH by human serum (●——●).

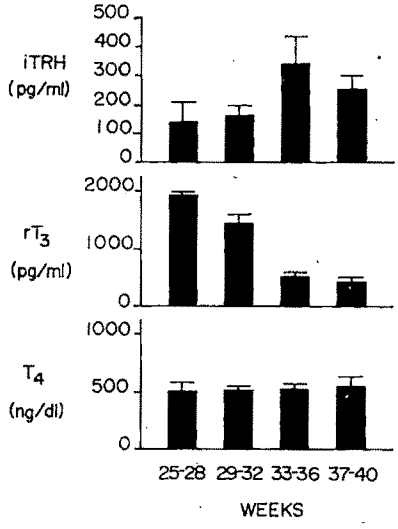


Fig. 3. Amniotic fluid levels of iTRH, rT_3, and T_4.

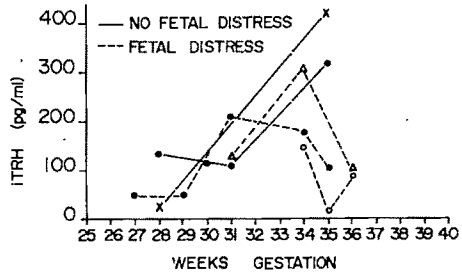


Fig. 4. Effect of advancing gestation on iTRH levels in patients from whom samples were taken on multiple occasions during pregnancy.

these levels during the last 8 weeks of pregnancy may be a marker for fetal or neonatal distress.

We have not shown whether the iTRH we are measuring is of the same size as the synthetic tripeptide or whether it is a larger precursor molecule. However, the degradation of amniotic fluid iTRH by serum is evidence that we are measuring a TRH-like substance as the immunoreactivity of the cross-reacting substances found in human urine is not destroyed by incubation with serum.[14]

We have confirmed earlier work showing that amniotic fluid rT_3 concentrations decrease during pregnancy and that T_4 concentrations are unaltered by advancing gestation.[6] Unlike Osathanondh and associates,[15] we did not find elevated rT_3 levels in patients with erythroblastosis fetalis. There was no correlation of iTRH levels with rT_3 or T_4 levels in amniotic fluid.

In conclusion, we have demonstrated the presence of immunoreactive TRH in amniotic fluid. The iTRH levels increase with increasing gestational age and preliminary evidence suggests that low iTRH levels in amniotic fluid may be a marker for fetal or neonatal distress.

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Lawrence D. Longo, M.D.

Traumatic intra-uterine adhesions

JOSEPH GUSTAV ASHERMAN
Journal of Obstetrics and Gynaecology of the British Empire, vol. 57, pp. 892-896, 1950

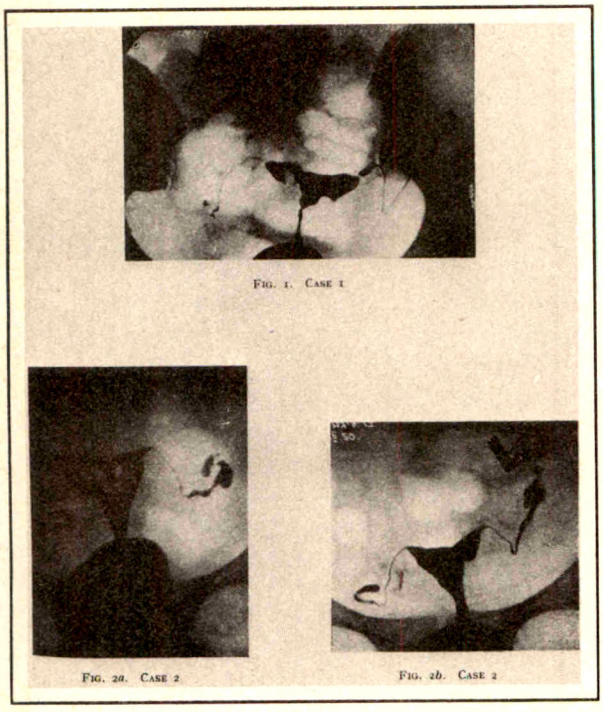


FIG. 1. CASE 1

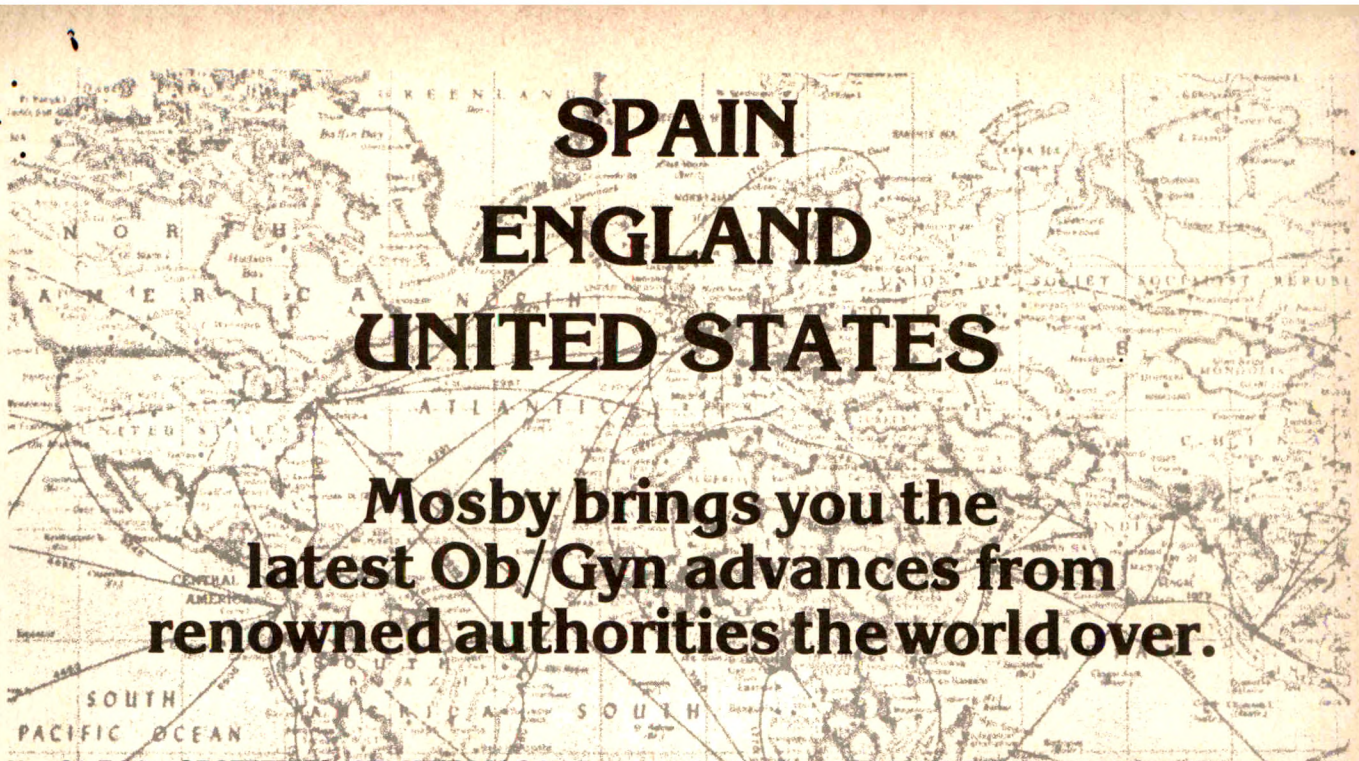
FIG. 2a. CASE 2

FIG. 2b. CASE 2

Adhesions between the anterior and posterior uterine wall as a cause of menstrual irregularities, infertility, and habitual abortion commonly are referred to by the eponym "Asherman's" syndrome. This is somewhat different from the lesion originally described by Asherman of Tel Aviv (Amenorrhoea traumatica [atretica], J. Obstet. Gynaecol. Br. Emp. 55:23, 1948), in which he detailed the findings in eight patients with secondary amenorrhea due to stenosis of the internal cervical os and reported a total of 29 such cases, the majority of which followed curettage for postpartum hemorrhage, incomplete abortion, or missed abortion. In this subsequent report Asherman first described regional obliteration of the uterine cavity due to partial conglutination of the opposing uterine walls. His first case (of eight reported) was of a 34-year-old woman who had experienced five spontaneous abortions during a 6 year period. Hysterography disclosed two filling defects of the uterine cavity (see illustration, *Fig. 1*). Thinking that the uterus contained submucous leiomyomas, Asherman performed a laparotomy and opened the uterus anteriorly. He then excised the unsuspected adhesions, placed a catheter from the endometrial cavity through the cervical os, and closed the incision. Subsequently the patient become pregnant and was delivered of a normal infant. That intrauterine adhesions indeed produced the hysterographic findings was demonstrated in his second case of a 35-year-old woman who had undergone five induced abortions followed by curettage for a missed abortion and infertility. The hysterogram disclosed a fenestrated cavity (see illustration, *Fig. 2a*), which, following hysterotomy with lysis of the adhesions, appeared relatively normal (see illustration, *Fig. 2b*). Asherman noted that he had discovered similar filling defects due to adhesions in 44 of 65 women examined for infertility following two or more curettages. He observed that adhesion formation seemed more frequently to follow curettage of old, organized placental tissue remains than curettage for recent abortion. Although Asherman employed a catheter to prevent readhesion of the uterine wall, he remained unconvinced as to its efficacy. (Later authors have recommended the use of a Foley catheter or intrauterine device for the same purpose.) Apparently, intrauterine adhesions with amenorrhea first were described by Heinrich Fritsch (Ein Fall von Volligem Schwund der Gerbormutterhohle nach Austkratzung, Zentralbl. Gynaekol. 52:337, 1894) in a 24-year-old woman with amenorrhea of 2 years' duration subsequent to a curettage performed 3 weeks after her first delivery. Fritsch was unable to introduce the smallest sound into the uterine cavity. He attempted to fashion a cavity by using a scalpel, dilator, and laminaria tent; however, within 2 weeks the cavity closed and the amenorrhea persisted. About the same time as Asherman's early reports, S. Stemer (Partial and

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total atresia of the uterus after excochleation, Acta Obstet. Gynecol. Scand. 26:263, 1946) and Henning Hald (On uterine atresia consequent to curettage, Acta Obstet. Gynecol. Scand. 28:169, 1949) published accounts of a similar nature. (The majority of authors believe that traumatic curettage 1 to 4 weeks post partum or after abortion and, to a lesser extent, infection are involved in the development of the adhesions.) Asherman published several other reports on this condition (Bull. Fed. Soc. Gynecol. Obstet. [Paris] 4:807, 1952 and Int. J. Fertil. 2:49, 1957) as well as on endometriosis and many other topics in gynecology. A native of Czechoslovakia, Asherman emigrated to Palestine in the 1920s and worked as a general practitioner. Following specialty training he ultimately became Chief of the Department of Obstetrics and Gynecology at the Hakyria Maternity Hospital in Tel Aviv. A leader in Israeli medicine, he founded the Israel Society of Obstetrics and Gynecology and was its president for many years.



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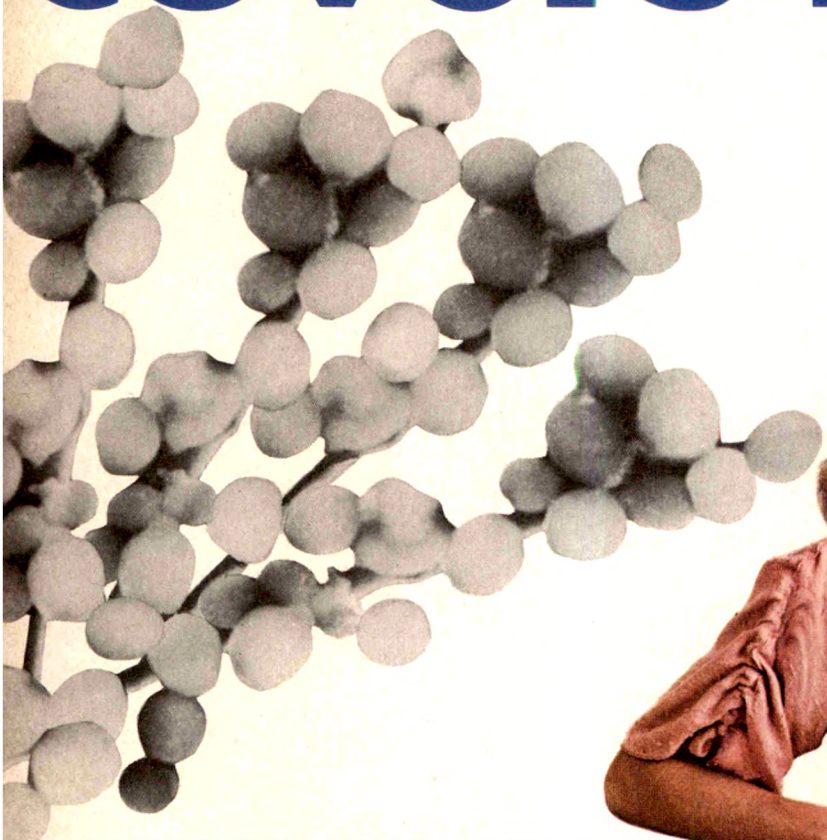
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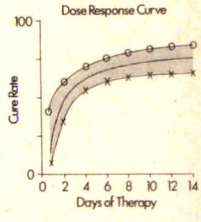
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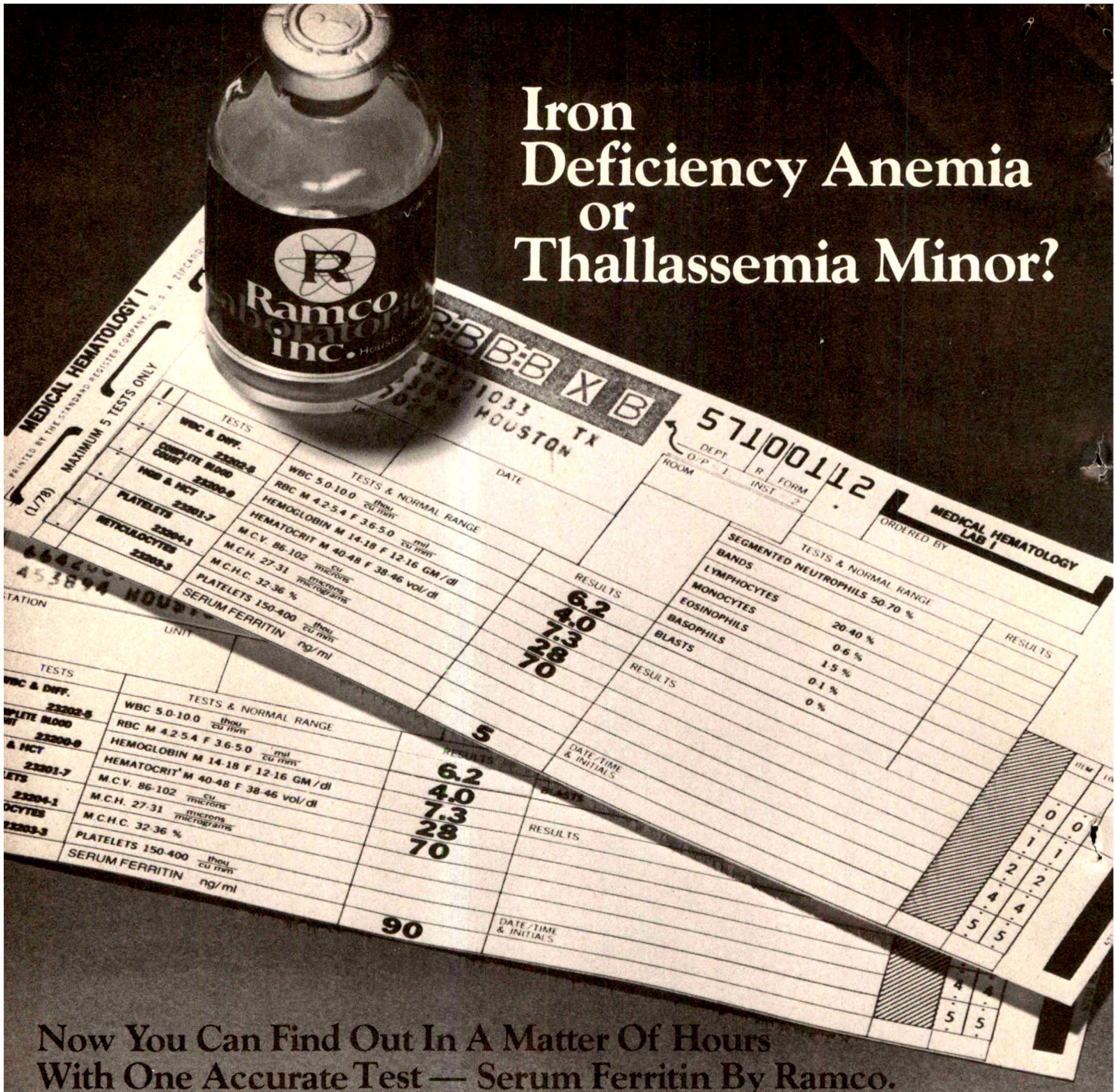
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CURRENT DEVELOPMENTS

Fetal breathing: A review

PETER LEWIS, M.D., PH.D., M.R.C.P.
PETER BOYLAN, M.B., D.C.H.*
London, England

The history, physiology, pharmacology, and clinical application of fetal breathing are reviewed. Early optimism that measurements of fetal breathing would aid in perinatal management decisions has remained unfulfilled. Problems to be overcome include standardization of technique and measurement parameters and allowance for physiologic variations. Recent research developments indicate that the likely role of fetal breathing in perinatal medicine will be in conjunction with other established tests of fetal health. (AM. J. OBSTET. GYNECOL. 134:587, 1979.)

FETAL BREATHING refers to fetal chest wall and diaphragmatic movements which mimic, in utero, the respiratory movements of postnatal life. Gaseous exchange is not part of the process and neither is alveolar expansion.

Although it was suspected at the turn of the century that fetuses made breathing movements in utero, confirmation of this awaited the development in the late 1960s of the chronic fetal lamb preparation by Dawes in Oxford and by Merlet in Paris. The subsequent short history of human fetal breathing research is a history of the development of ultrasound technology.

Indeed, it is arguable that the most significant development in fetal breathing research is about to occur almost unnoticed by the academic research worker. As of late 1978, more than a thousand real-time scanning units have been brought into clinical use in North America. User enthusiasm and mass production will ensure that the number will rapidly increase.[1] In consequence observation of fetal breathing movements is no longer the prerogative of the physiology laboratory or the university clinic; fetal breathing can and will be observed in every obstetrician's office. Even the novice scanner struggling to measure fetal biparietal diameters will scarcely fail to notice whether or not his fetal patient is making breathing movements. What then is the obstetrician to make of this new physical sign? He will wish to know the significance of breathing or not breathing, how this relates to the circumstance of measurement, and whether his observations should alter his management. This paper attempts to review present knowledge of fetal breathing in this practical context.

From the Department of Clinical Pharmacology, Royal Postgraduate Medical School, Hammersmith Hospital.

Supported by The Ciba Chemie Foundation for Therapeutic Research and The Wellcome Trust.

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History

The first graphic records of fetal breathing movements are attributed to Ahlfeldt and Weber at the end of the nineteenth century.[2] In 1888, they observed rhythmic fetal movements through the maternal abdomen and attributed them to attempts by the fetus to breathe. Ballantyne,[3] in a text published in 1902, gave an eloquent description of the physiologic nature of fetal breathing movements and stated that several other workers had observed and obtained graphic records of breathing in utero. He noted the movements to be of two types; the first, a series of sharp elevations

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and depressions, were attributed to hiccups, while the second, a series of undulations, were attributed to regular interuterine respiratory movements. Windle,[4] in 1940, observed fetal respiratory efforts in a variety of animal species at cesarean section but concluded that these movements were a reaction to abnormal stimuli. Barcroft,[5] in 1946, arrived at similar conclusions following observations of sheep fetuses. In fetuses observed through the transparent amniotic sac and delivered into a warm saline bath, breathing movements could be elicited from day 35 to day 60 by tactile stimuli. Term gestation in the sheep is 147 days. After 50 days of age spontaneous fetal body movements initiated breathing movements, but from 60 days on fetal breathing movements could be provoked only by asphyxia. Barcroft concluded that the development of fetal breathing was related to the functional development of the nervous system and that once the ability to perform regular breathing movements was attained the fetus rested until delivery. These early experimenters had no method of performing long-term observations on fetal sheep.

In the late 1960's, Dawes and his group[6] in Oxford repeated Barcroft's observations using recently developed experimental techniques. Fetal lambs were delivered into a warm saline bath under maternal epidural anesthesia, or catheters and electrodes were inserted and the fetus was replaced in the uterus. Using these techniques the Oxford group undertook many basic measurements on the arterial pressure of the fetus, the movements of fluid in the trachea and esophagus, the amniotic pressure, and the electrocortical and transorbital potentials. A similar approach was being adopted at this time by Merlet and colleagues[7] in Paris. Observations made during the course of these experiments form the basis of present-day knowledge of fetal breathing. The existence of breathing movements in the sheep fetus was confirmed and these were seen to be a spontaneous physiologic phenomenon even in late pregnancy.

In 1971, Boddy and Robinson[8] described the application of A-scan ultrasound to the observation and measurement of fetal breathing in the human. By 1975, the A-scan technique had been used to observe breathing movements of 200 fetuses in labor and more than 500 antenatally.[9] Breathing movements were detected as early as 11 weeks' gestation and after 36 weeks a regular pattern was detected, similar to that seen in postnatal life. The movements were present from 55% to 90% of the time, until the approach of labor when the incidence fell. A diurnal rhythm was described, which resembled that seen in the fetal sheep.

Fasting reduced the incidence of fetal breathing while intravenous glucose given to fasting women stimulated breathing movements. Altered patterns of fetal breathing, both antenatally and during labor, initially held great promise as a method of detecting fetal compromise and, therefore, preventing perinatal hypoxia. However, these preliminary results were, in the words of the authors, "almost too good to be true" and they advocated independent verification of their tentative conclusions.

The A-scan technique for the detection of fetal breathing movements is tedious, relying as it does on the fetus' remaining in one position. Various other fetal and maternal movements produce records similar to those produced by breathing. The limitations of the technique are well outlined in the paper of Farman and associates[10] who recommended further technical sophistication before the method could be said to provide reliable information. Various attempts were used to improve A-scan methods, including the use of a double-beam scan,[11] but none of these was totally successful in eliminating artifact.

The development of real-time, gray-scale B-scan machines was a major advance. These systems consist of a multiple array of ultrasonic transducers which allow video reconstruction of a cross section of the uterine contents in real time. Therefore, a moving, rather than static, image is available for observation. The application of the method to the study of fetal breathing movements was first demonstrated by Gennser in Oxford and by Fox and Hohler[12] in the United States, around the end of 1975. Despite the fact that current machines have a spatial resolution limited to 0.5 mm, similar to the smallest chest wall movement of the fetus, the resolution is in practice sufficient to detect very small chest wall movements. This is because with every breath a characteristic visual cue is given not only by the chest wall of the fetus but also by structures moving within it. In the last three years many observations of human fetal breathing have been made using real-time ultrasound and the subject has undergone re-evaluation. Many of the earlier hopes that the study of fetal breathing movement would give a good indication of fetal health are having to be reassessed.

Fig. 1 illustrates the chest wall movements seen using this technique. The chest wall movements are of small amplitude and very difficult to detect when viewed as still photographs. When the chest is viewed in real time, however, the associated cues of changing lung density make their movements readily identifiable. The figure shows the chest and head of a 26 week fetus.

One other ingenious method has been used to investigate human fetal breathing. This is based on the observation that when the fetus makes breathing move-

ments high-velocity Doppler shift signals are generated within the fetal chest and upper abdomen.[13] These signals are generated either by jetting of venous blood in the inferior vena cava across the diaphragmatic hiatus or from blood flow changes in the umbilical vessels coincident with breathing movements.[14] It transpires that many clinicians have heard fetal breathing movements while using ultrasound echocardiography and dismissed the signals as artifacts. However, despite the simplicity of the method, observing fetal breathing by Doppler ultrasound has not gained a following as wide as that of those methods employing direct visualization of the fetal chest wall by real-time ultrasound.

Physiology of fetal breathing

Animal studies. Dawes and associates[6, 15, 16] published their findings in the now classic papers of the early 1970s. They concluded that fetal breathing movements were normally, but intermittently, present in the fetal lamb over the greater part of gestation.

Fetal lambs delivered into a warm saline bath exhibited brief outbursts of spontaneous, irregular respiratory activity, from 40 days' gestation onward. In the chronic fetal sheep preparation tracheal pressure changes were observed which were independent of amniotic pressure changes; the most likely explanation was fetal breathing. A continuous record of fetal diaphragmatic activity confirmed that contractions of the diaphragm were responsible for the changes in tracheal pressure.[17] Tactile stimuli to the face also elicited what appeared to be a primitive rooting reflex, previously described by Barcroft,[5] and an expiratory effort. With advancing gestational age the depth and frequency of the movements increased.

Two types of movement were described, single inspiratory efforts, or gasps, and bursts of rapid irregular activity. Gasps were present for approximately 5% of the observed time and occurred in episodes lasting a few minutes. They had a frequency of 1 to 4/minute and an amplitude of 20 mm Hg and more. Asphyxial gasps were regular, more prolonged, and deeper than those described above. Episodes of rapid irregular breathing were of much higher frequency and lasted from a few seconds to an hour; inspiratory efforts were irregular in both rate and depth.

The characteristic circadian rhythm was noted. The peak incidence of fetal breathing was in the late evening while fewest movements were made toward dawn. This diurnal variation was noted to be present from 85 days' gestation onward. Simultaneous electroencephalographic recording showed that rapid fetal breathing movements were always associated with low-voltage, rapid-frequency electroencephalographic activity.

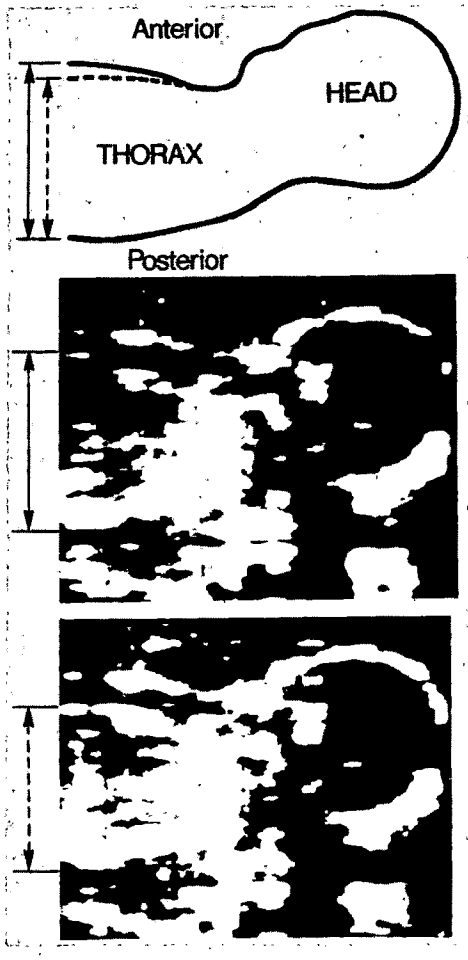


Fig. 1. Fetal breathing movements in a 26 week human fetus as observed by two still photographs from a real-time scanning sequence showing maximal inspiration *(I)* and expiration *(E)*.

There was no such association with gasping. Electrodes designed to detect eye movements revealed that rapid eye movement (REM) sleep was associated with the same electroencephalographic activity. The electrocortical characteristics of REM sleep are well developed only after 125 to 130 days' gestation in the sheep; therefore, it was apparent that rapid, irregular fetal breathing occurred in the absence of such electrocortical activity in the early stages of pregnancy.

Blood gas concentrations over the range of spontaneous variations encountered did not influence fetal breathing in any way. In addition cervical vagosympathetic trunk section or blockade with a local anesthetic drug had no effect on the movements. Dawes concluded that, under physiologic conditions, neither pulmonary stretch receptors nor central or peripheral chemoreceptors played any part in regulation of fetal breathing activity.

The effects of hypoxia and hypercapnia were then studied. Reducing fetal arterial Po_2 from its mean

normal of 25 to 16 mm Hg abolished rapid irregular fetal breathing. When there was also a fall in arterial pH the recovery period was much prolonged. The electroencephalogram during hypoxia showed a slow, large-voltage pattern characteristic of quiet sleep.

Increasing fetal arterial Po_2 up to 35 mm Hg had no effect on the character or incidence of breathing movements. Therefore, oxygen supply was not felt to be a limiting factor.

Hypercapnia caused a sustained increase in fetal breathing. Raising the fetal arterial Pco_2 by 8 to 10 mm Hg doubled tracheal fluid flow and the proportion of time during which fetal breathing movements were present.

During rapid, irregular fetal breathing tracheal fluid movement was minimal, fluid displacement amounting to no more than 0.5 ml per breath compared with approximately 80 ml of air after birth. This finding was consistent with the relatively high density and viscosity of the fluid. Between episodes of breathing there occurred, once or twice an hour, an outward flow of approximately 2 ml associated with a brief rise in tracheal pressure. Net tracheal flow was in an outward direction and near term could amount to 100 ml/kg/day.

Breathing movements were associated with cardiovascular changes. Rapid, irregular breathing was accompanied by tachycardia, a rise in carotid pressure, and an increase in aortic flow. Expiratory efforts were accompanied by a fall in heart rate and carotid pressure and a decrease in aortic flow. Dalton and colleagues[18] more recently have found an increase in heart rate variability during episodes of fetal breathing; they concluded, however, that it is not possible to identify episodes of breathing from characteristic fetal heart rate changes.

Fetal hypoglycemia, <10 mg glucose/100 ml, inhibited breathing activity. In sheep studies there was insufficient diurnal variation in blood glucose levels to account for the circadian rhythm of fetal breathing activity. Handling and light general anesthesia also inhibited fetal breathing.

Three of the ewes studied went into spontaneous labor during the course of the experiments; none showed a significant change in rapid, irregular breathing before the onset of labor. In one lamb fetus the record during labor was of sufficiently good quality to allow analysis and in this fetus breathing movements were significantly reduced during labor.

Fetal breathing movements under physiologic conditions have been measured directly in several other species, including the goat[19] and the monkey.[20] In all species studied the movements have been periodic rather than continuous, with bursts of breathing interspersed with periods of apnea. The incidence of breathing at term varies among species, ranging from 40% in the lamb to 80% in the monkey.

Breathing patterns before death in a group of 16 lambs have been described by Patrick and associates.[21] Three patterns were noted. In all there was a prolonged apneic interval between cessation of normal fetal breathing and onset of antemortem patterns.

In six of the fetuses there was a continuous "picket fence" pattern of rapid, regular breathing which continued until a few minutes before death in all but one fetus; all those with the "picket fence" pattern had hypercapnia. In eight there were episodes of gasping with a background of apnea; as death approached the frequency and amplitude of the gasps increased. In the third pattern, noted in two lambs, there were episodes of rapid breathing accompanied by gasping, again with a background of apnea. A similar response, apnea followed by isolated gasps, was also noted by Tchobroutsky and colleagues,[22] who asphyxiated fetal lambs with an inflatable cuff around the umbilical cord. Manning and co-workers[23] observed terminal gasping in a series of seven rhesus monkey fetuses that died. However, in these monkeys the "picket fence" pattern was absent and they feel that this may be because panting is not a characteristic breathing pattern in nonungulate species. Panting has been observed in exteriorized lambs by raising the bath temperature 1° C from 39.5° C.[16] Boddy[24] reported that Robinson observed similar episodes in the human associated with a rise in maternal temperature.

Chapman and associates[25] have recently reported on patterns before death in six lamb fetuses which subsequently died before labor. In all six a period of apnea preceded the abnormal patterns before death. One fetus had isolated gasps with a background of apnea. In three fetuses the apneic interval was followed by episodes of regular, rapid breathing with interspersed gasps; these episodes merged into a uniform continuous pattern. In the remaining two fetuses there were episodes of gasping which progressively lengthened and eventually merged into the uniform continuous pattern described above. The various patterns are represented graphically in Fig. 2

In all animal species so far described the prognostic significance of a period of apnea followed by either gasping or rapid continuous breathing is apparent. Dawes has emphasized, however, that such patterns do not inevitably terminate in death and that recovery is possible.

In conclusion, therefore, fetal breathing movements in the nonhuman occur intermittently from an early stage of gestation and become more organized as term

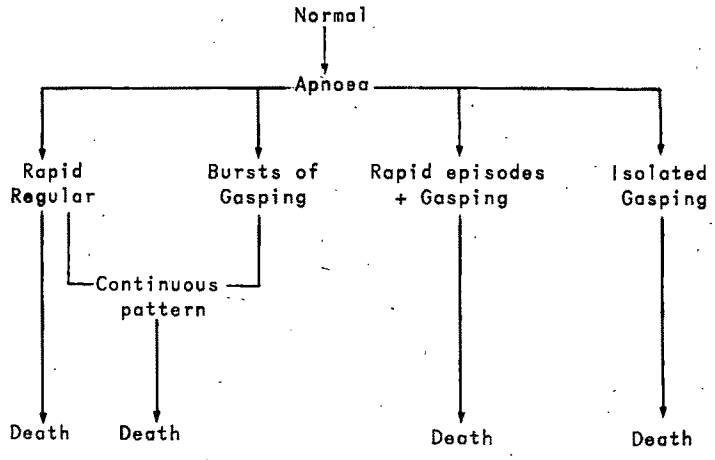


Fig. 2. Changes in fetal breathing behavior in lambs prior to intrauterine death as observed by recording tracheal pressure (Modified from Chapman and associates.[25])

approaches. They are not influenced by changes in blood gas concentrations over the physiologic range but are markedly inhibited by anoxia and stimulated by hypercapnia. Hyperoxia has no effect. Handling, light general anesthesia, and hypoglycemia inhibit fetal breathing. Tracheal fluid oscillations are minimal during normal fetal breathing but with gasping, amniotic fluid, with or without meconium, is inhaled as far as the matured bronchial structure allows. Normally there is a net outward flow of tracheal fluid which increases toward term and is reflected in the increasing amounts of surfactant found in the amniotic fluid.

Fetal death is associated with particular patterns, the most characteristic preceding feature being prolonged apnea. Labor appears to be associated with inhibition of fetal breathing but in the very small series reported the movements do not appear to decrease with the approach of labor. It must be borne in mind, however, that almost all the above conclusions have been derived from work on the fetal lamb and other species have been much less studied.

Human pregnancy. Boddy and Robinson were the first to describe the characteristic features of human fetal breathing; all their observations were performed using the A-scan technique. They observed breathing movements from 11 weeks' gestation; by 36 weeks the pattern was regular, similar to breathing movements in postnatal life. Breathing movements were present during 30% to 90% of any recording period. A circadian rhythm similar to that reported in the fetal sheep was present with a minimum amount of breathing movements in the early morning. Hypoglycemia was associated with a decrease in breathing and intravenous glucose given to fasting mothers stimulated fetal breathing within 10 minutes.

Antenatally the presence of normal breathing movements for less than 50% of the time, accompanied by some gasping, was felt to predict the probable development of fetal distress in labor. Patterns leading up to fetal death were described in 11 fetuses; in 10 there were gasping movements only; in one fetus of a diabetic mother there were short bursts of unusually rapid breathing in the 2 days prior to death.

In labor normal fetal breathing movements were noted for 60% to 90% of the time if the maternal P_{CO_2} was normal or raised and if there was no hypoxia; if the P_{CO_2} fell because of hyperventilation then movements were reduced in incidence but there was no gasping. Asphyxia was accompanied by the cessation of normal breathing and onset of gasping.

Real-time ultrasound. Certain of the above characteristics of human fetal breathing have not been confirmed using real-time ultrasound. Dawes has suggested that the A-scan results need to be re-evaluated critically using real-time scanning. Since the first reports by Gennser in 1975 several papers have been published which do not corroborate the original A-scan findings. The advantages of real-time ultrasound were described by Fox and Hohler,[12] who noted the easier orientation, more precise definition of the timing of events, and elimination of movement artifacts; they compared A-scan and real-time results and found that real time gave a satisfactory record 95% of the time after 20 weeks' gestation whereas the A scan resulted in reliable images 28% of the time before 28 weeks and 66% of the time after 28 weeks. Longitudinal midline alignment gave the most satisfactory orientation for accurate scoring of fetal breathing although some workers prefer a transverse scan through the fetal thorax.

Fetal breathing in normal pregnancy. A very wide range in incidence of fetal breathing in normal pregnancies has been observed by several workers. The incidence

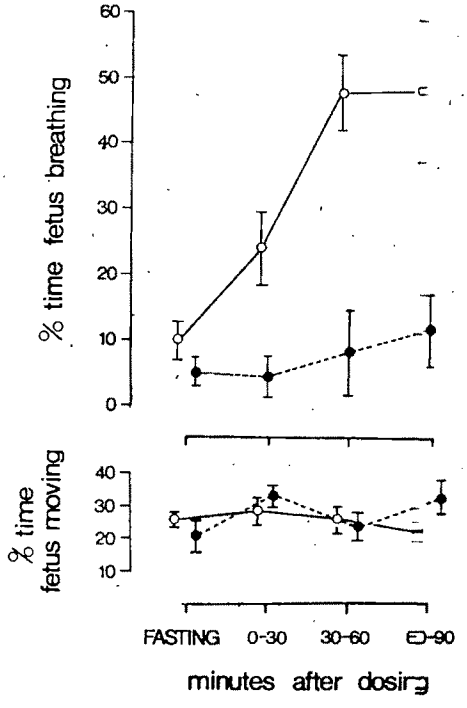


Fig. 3. Fetal breathing and fetal whole body movements following maternal ingestion of 50 gm oral glucose and water in equivalent volume. Six patients in each group, 36 weeks' gestation.

may range from 90% to none in the observation period, generally 30 minutes. In contrast to the A-scan findings, prolonged periods of apnea are compatible with a satisfactory perinatal outcome.

Patrick and associates[26] studied a group of 10 normal fetuses between 09.00 and 17.00 hours at 34 to 35 weeks' gestation. The mean hourly incidence of breathing activity increased during the day from 16% before noon to 35% in the 5 hours after noon. Periods of apnea lasted up to 20 minutes. Fetal hiccups were seen at least once in every fetus during the 8 hours of observation time.

Fox and Hohler[12] examined 24 normal patients and found a mean incidence of 30%, with a range of 98% to complete apnea. As gestation advanced the incidence of fetal breathing movements appeared to increase; Angel and associates[27] noted an increase from 5% at 25 weeks to 43% at term.

Because of the known inhibitory effect of hypoglycemia on fetal breathing, Trudinger and associates[28] standardized the observation period by giving a 50 gm glucose drink to the mothers 30 minutes prior to observing the fetus for a period of 30 minutes. In 12 normal fetuses breathing movements were present for 40% to 70% of the observed time. In fetuses of fasting mothers breathing activity was present for no more than 10% of the time. Fig. 3 illustrates the responses of a group of normal 36 week fetuses to maternal ingestion of 50 gm of glucose. While ingestion of water had no effect on either breathing or fetal movements, glucose quadrupled breathing and had no effect on other fetal movements. Natale and associates[29] have recently obtained similar results in a group of 22 healthy patients in late pregnancy.

Fox and Hohler[12] looked at the influence of an oral glucose load given to fasting and nonfasting mothers. They studied 18 nondiabetic patients; nine were fasting and the incidence of fetal breathing increased from less than 30% to more than 60% following the glucose. In the nine patients who were not fasting there was no difference before and after the oral glucose, although the initial amount of breathing was greater in the fetuses whose mothers were not fasting.

Patrick and associates[26] noted that the percentage of time spent in breathing increased from 18% to 43% following an 800 calorie meal; maternal blood sugar levels were not estimated during this study. In the same paper they described some observations on diabetic pregnancies; breathing movements were present more than 80% of the time with maternal glucose concentrations greater than 180 mg% while the same fetuses breathed less than 5% of the time with maternal glucose concentrations of 40% to 50 mg%.

Roberts and associates[30] examined 16 normal patients throughout the 24 hour period; scanning was done for 1 hour every 3 hours. The incidence of fetal breathing ranged from 11% to 61% (mean 30%). A marked diurnal variation was noted with a peak in the early afternoon and trough in late evening and early morning. Fetal breathing increased in rate, depth, and amount following meals; a significant correlation was found between the incidence of fetal breathing and plasma glucose levels and between rises and falls in the plasma glucose level.

However, Angel and associates[27] found no correlation between blood glucose and the incidence of fetal breathing in a series of 21 patients observed through pregnancy from 18 weeks' gestation to term. Similarly, in diabetic patients, McCune[31] found no correlation between breathing and maternal blood glucose concentration. Table I summarizes published work on normal subjects.

From the reported studies on the influence of glucose on fetal breathing movements it appears that maternal fasting and hypoglycemia inhibit fetal breathing movements, and a rapid increase in maternal, and, therefore, presumably fetal, blood glucose concentration stimulates breathing movements. In the nonfasting mother there does not appear to be a correlation as direct as that with maternal blood glucose status. The

physiologic mechanisms involved in this interaction between swings in blood glucose concentration and fetal breathing are not understood. Human fetal breathing activity may be a reflection of neurological maturity, with an immature respiratory center being overly sensitive to hypoglycemia. In this context it is interesting to note that in the neonate hypoglycemia may be responsible for apneic attacks.[32] Studies on the fetus of the diabetic mother might help to explain this relationship.

Blood gas alterations. Hypercapnia and hypoxia have profound influences on breathing in the fetal sheep. Ritchie[33] has studied the influence of hypercapnia in the human; maternal hypercapnia, induced by breathing 5% carbon dioxide in air, increased the incidence of fetal breathing threefold in 52 of 54 normal fetuses. Maternal hyperoxia had no effects on the incidence of breathing in a group of 32 normal fetuses. Van Weering and associates[34] obtained similar results in a group of 25 normal patients.

Fetal hiccups. Fetal hiccups, or singultus fetalis movements as Bots and associates[35] call them, which are often noticeable by the mother, have been described by Lewis and Trudinger,[36] by Lemay and associates,[37] and by Patrick and associates.[26] They are apparently a normal phenomenon although Bots and associates have recently pointed out that they were present in greater frequency in a group of low–birth weight infants; the difference was not statistically significant and they advocated further examination of the phenomenon. Dunn[38] pointed out that a similar type of movement had been described in 1902 by Ballantyne.[3]

Fetal presentation. Marsal and associates[39] using A scan, formed the impression that fetal presentation influenced the incidence of breathing movements. They found a reduced incidence in the leading twin in a cephalic presentation but not in a breech presentation. They also found less breathing in singleton pregnancies where the presentation was cephalic compared with breech and concluded that pelvic side wall pressure on the fetal head exerted an inhibitory effect on fetal breathing activity. However, Angel and associates,[27] using the real-time system, more recently found no such differences. This is a further example of discordance between results from the A scan and those from real-time scanning.

Amniocentesis. Manning and associates[40] noted a significant decrease in fetal breathing activity for up to 2 days following amniocentesis in a group of 24 high-risk pregnancies.

Fetal breathing in labor. The initial reports from the Oxford group of workers concerning fetal breathing in labor, measured with the A scan, have not been substantiated with the real-time system.

Table I. Fetal breathing in normal subjects

Study	*No.*	*Weeks' gestation*	*Time fetus spent breathing (%)*
Patrick et al.[26]	10	34-35	32
Fox and Hohler[12]	24	20-41	31
Roberts et al.[30]	16	30-39	30
Angel et al.[27]	21	25	5
		30	20
		37	35
		Term	43
Trudinger et al.[28]	12	34-48	10 (Fasting)
			55 (After glucose)
Fox and Hohler[12]	8		60 (After glucose)

Wittman and associates[41] reported on a group of 25 patients studied in labor between 8 AM and 4 PM. Nine of the labors were spontaneous and 16 were induced. The patients fasted for at least 16 hours although the mean blood glucose level was 91 mg%; 20 of the patients were receiving a 5% dextrose infusion. Breathing was observed in 13 of the 25 fetuses and tended to occur in episodes shorter (up to 30 seconds) than those of movements observed antenatally. They found a significant correlation between a decrease in the amount of fetal breathing and an abnormal fetal heart rate tracing (an abnormal fetal heart tracing was defined as having poor variability, late or severe variable decelerations, or bradycardia). Fetal hiccups were observed in three of the 25 subjects.

We have also studied women in labor. Of 10 patients in induced labor only three exhibited regular fetal breathing. Two of these patients were receiving a dextrose infusion. Blood glucose concentrations were 284 and 85 mg% respectively. A period of hiccupping was seen in one further patient. In the remaining six patients in whom no fetal breathing movements were seen the mean maternal blood glucose level was 71 mg%. All the patients were delivered of healthy infants of appropriate weight for gestational age and none developed any perinatal problems. These results indicate that absence or paucity of fetal breathing in induced labor is compatible with a satisfactory perinatal outcome. In addition they point to a possible etiologic role of maternal blood glucose in the control of fetal breathing in labor. It is worth noting that labor was induced with intravaginal prostaglandin E_2.

Pharmacology of fetal breathing

Animal pharmacology. All quantitative work on the animal pharmacology of fetal breathing has been carried out in sheep, usually in chronic preparations in which the fetal trachea was catheterized. Boddy and associates,[42] in 1976, carried out a careful study of the effect of small doses of pentobarbital (4 mg/kg intrave-

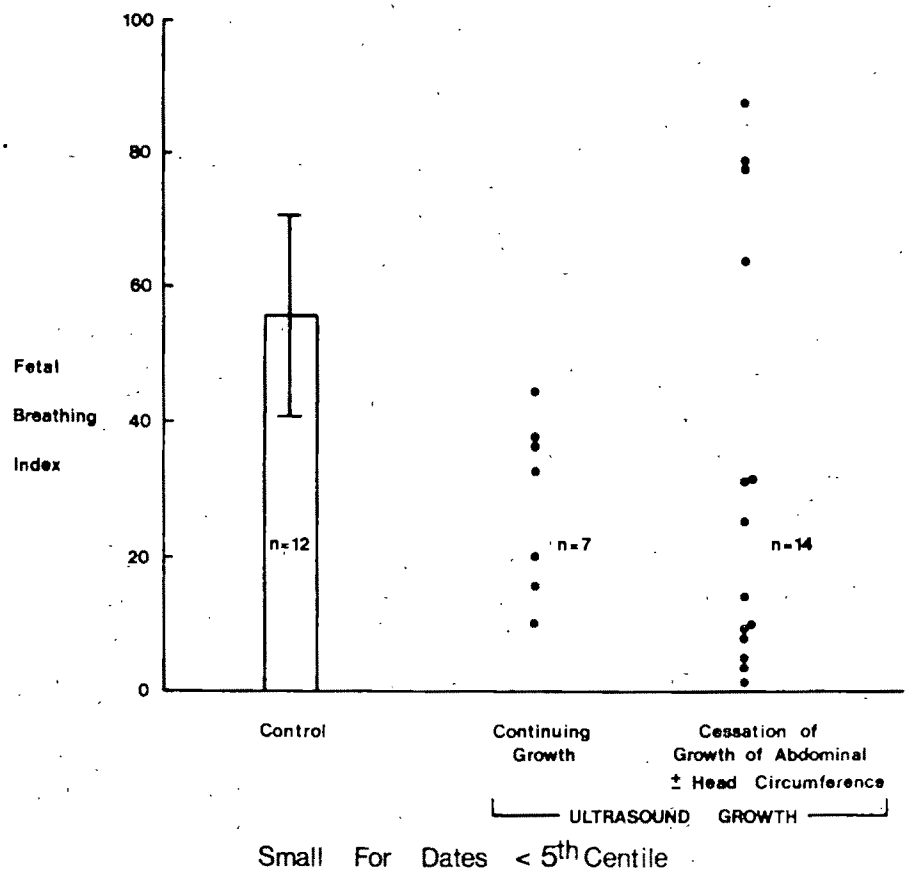


Fig. 4. Proportion of a 30 minute observation period which fetuses spent breathing, 30 minutes following maternal ingestion of 50 gm oral glucose. All fetuses were subsequently born small for dates (less than the fifth percentile, apart from the control group). (From Trudinger et al, 1978.[28])

nously) given to sheep in the last third of pregnancy. This small dose of barbiturate had little apparent effect on the ewe but markedly diminished fetal breathing movements. The effect of a single dose lasted approximately 2 hours and coincided with a change to a high-voltage pattern in the fetal electrocorticogram. The time to arrest of fetal breathing following administration of pentobarbital varied with gestational age. It is interesting that in similar experiments doses of meperidine (1 to 3 mg/kg) had no consistent effect on fetal breathing movements. However, when fetal breathing had been augmented by inducing maternal hypercapnia subsequent dosing with meperidine reduced breathing by the fetus.

Condorelli and Scarpelli[43] in similar experiments also reported that various barbiturates injected into the fetus and into the ewes stopped respiratory movements by sheep fetuses in late gestation.

Piercy and associates[44] studied the effects of diazepam. Maternal intravenous infusion of diazepam in a dose of 0.18 to 0.22 mg/kg reduced the incidence of fetal breathing movements. The time course of this reduction was reproducible and breathing returned to preinjection levels about 60 minutes after dosing. These authors also studied the effects of caffeine and doxapram. Both of these drugs stimulated fetal breathing. When caffeine (1.5 to 5 mg/kg) was administered directly to the fetus, breathing was transiently stimulated for 3 to 5 minutes. Doxapram also initiated fetal breathing when given directly to the fetus in a dose of 1 to 2 mg/kg. Hogg and co-workers[45] also reported that maternal infusion of doxapram stimulated fetal breathing movements in the sheep.

Pilocarpine in small doses stimulates fetal breathing movements in the sheep. Brown and colleagues[46] feel that the effect is mediated through sensitization of carotid sinus chemoreceptors. Atropine and carotid sinus nerve ligation abolish the response.

Human pharmacology. Most pharmacologic studies carried out in human pregnancy have been done in patients actually being treated with the substance under investigation and were in the nature of incidental observations. With the exception of the study of Marsal and associates[47] on betamethasone, these

human studies have not included control or placebo experiments. Since fetal breathing is not a stable activity it is possible that some of these drug effects might have been due to the lapse of time or the psychological effect of the mother's being alarmed or reassured by the treatment she was receiving. However, most of the results in human pregnancy accord well with the concept developed in sheep, namely, that central nervous system depressants decrease fetal breathing while respiratory stimulants increase it.

Adrenocortical steroids.

BETAMETHASONE. Marsal and co-workers[47] investigated 29 pregnant women between the twenty-ninth and thirty-fifth weeks of pregnancy who were at risk of preterm delivery. Nineteen of these women were treated with 12 mg betamethasone daily while 10 served as controls. The incidence of fetal breathing movements was similar in both control and treated groups, implying that the steroid had no effect on fetal breathing activity and that its effect, if any, on surfactant production is mediated by other mechanisms.

Narcotic analgesics.

MEPERIDINE. Gennser and colleagues[48] reported the results of meperidine, 1 mg/kg, administered to a group of five women before the onset of labor. There was a decrease of about 50% in fetal breathing movements. Lewis and Oliver[49] performed a double-blind investigation on six normal nonsmoking primigravid patients between 34 and 35 weeks' gestation. Following an overnight fast the women were given a 25 gm glucose drink; after 30 minutes' control scanning the women received, in a double-blind manner, either intravenous meperidine or intravenous saline. The results showed that 5 mg intravenous meperidine had no discernible effect on fetal breathing movements, and there was no effect of placebo.

Benzodiazepines.

DIAZEPAM. Boddy[50] examined the effect of 20 mg diazepam given intramuscularly and found that it caused a marked reduction in fetal breathing.

Lewis and Oliver,[49] using the same protocol they used with meperidine, found that 2 mg diazepam given intravenously had no discernible effect on fetal breathing. Again there was no effect from injecting the saline placebo. Gennser and associates[48] showed that intravenous and intramuscular injection of diazepam had little effect on fetal breathing.

Barbiturates.

AMYLOBARBITAL. Boddy[50] reported that amylobarbital had little effect on fetal breathing.

Selective β_2-receptor stimulants.

SALBUTAMOL. Lewis and Oliver[49] have studied oral salbutamol in doses of 4 and 8 mg. Normal, primiparous, nonsmoking patients were studied between 34 and 38 weeks. The patients were fasting and no glucose was given to them during the course of the experiment. Placebos were not included since the previous work with diazepam and meperidine had shown no placebo effect. Six patients were studied for each dose of salbutamol for half-hour periods from 30 to 60 and 90 to 120 minutes after drug administration. Salbutamol was chosen for investigation because work by Gennser and colleagues[48] suggested that terbutaline had a stimulatory effect on fetal breathing, because stimulation of β_1-receptors in the adult increases respiratory rate and because salbutamol is a mildly hyperglycemic agent.

The results show that salbutamol, either 4 or 8 mg, had no effect on fetal breathing activity. Salbutamol also had no effect on fetal movements. This was unexpected since it has been reported that when women are given large oral doses of salbutamol they often complain of excessive fetal movement. This may be another illustration of the difference between the activity of normal and compromised fetuses.

TERBUTALINE. Gennser and colleagues[48] reported that in one case of terbutaline infusion to a woman in labor fetal breathing movements were stimulated.

Antihypertensive agents. Boddy has reported that methyldopa diminished fetal breathing in some patients to whom it was given but this was not a consistent effect. Methyldopa is known to regularly produce sedation in laboratory animals and man. However, it has also been reported to increase REM sleep in man.[51]

Smoking. Manning and co-workers[52] studied 19 women with uncomplicated pregnancies between the thirty-second and thirty-eighth weeks. They showed that smoking two cigarettes caused a marked fall in the proportion of time that fetal breathing movements were observed. The effect lasted up to two hours.

Manning and Feyerabend[53] showed that the fall in fetal breathing movements was significantly related to the rise in maternal plasma nicotine after smoking but not to the rise in carboxyhemoglobin. The nicotine effect was thought to be placental rather than fetal since nicotine given to fetal lambs stimulated rather than depressed breathing.

Gennser and associates[48] presented results to show that cigarette smoking and chewing nicotine containing gum decreased fetal breathing activity.

Caffeine. Finally, Lewis and Oliver[49] studied the effect of 50 mg of caffeine given orally in a study using six patients. Caffeine had no effect on fetal breathing or body movements.

Conclusions. The first conclusions from these studies on human fetal breathing and the effect of drugs are that the human fetus is not as exquisitely sensitive to

Table II. Correlation of fetal breathing movements with outcome of pregnancy

Study	*Type of test*	*No.*	*Correlation with outcome*
Fox and Hohler[12]	FBM in pts with positive OCT.	7	Good
Manning et al.[54]	FBM with CTG	223	Good
McCune[31]	FBM alone	90	Poor
Van Weering et al.[34]	FBM with maternal hypercapnia and hyperoxia	26	Good
Manning[57]	FBM alone	25	Good
Trudinger et al.[28]	FBM following 50 gm glucose	50	Good
Roberts et al.[30]	FBM alone—24 hour study	5	Good

FBM: Fetal breathing movements. CTG: Cardiotocography.

central nervous system depressant drugs as has often been thought. Some of the less well-controlled data on depressants in human pregnancy are questionable. In the normal fetus it seems that fetal breathing is a stable activity much more influenced by maternal plasma glucose than by sedative or stimulant drugs.

Fetal breathing in abnormal pregnancy. There have been several studies performed on abnormal pregnancies but, again, none has provided conclusive confirmation of the earlier A-scan results of Boddy and Robinson. The range of incidence of fetal breathing in both normal and abnormal pregnancies is such that prediction of outcome in the individual fetus is almost impossible, using fetal breathing measurements as the sole index of fetal health. Fox and Hohler[12] and Manning and associates[54] have recently presented data combining fetal breathing measurements with some other test of fetal health, with results more promising than those with fetal breathing movements alone.

In obstetrics the term "high-risk" encompasses a multitude; previous obstetric history and events in the present pregnancy combine to place patients in this category. The term is usually meant to refer to fetal risk of death in utero or perinatal hypoxia with all its attendant long-term problems. Maternal hypertension of pregnancy, with a diastolic pressure not greater than 100 mm Hg and no proteinuria, has been shown not to be injurious to fetal health.[55] Nevertheless many series of high-risk pregnancies include just such patients. Similarly, retrospective analysis of fetal heart rate tracings in labor and classification as "abnormal" are meaningless in the absence of accompanying data on scalp pH.[56] Perhaps the results of antenatal screening might be better if only those fetuses truly "at risk" of dying or developing perinatal hypoxia were included in the abnormal group.

Fox and Hohler[12] presented their findings in seven patients with positive oxytocin stress tests (OCT). Two of these fetuses had no fetal heart rate acceleration with fetal movement; one had prolonged apnea, while the other exhibited gasping movements; both had poor perinatal outcomes. The other five fetuses had fetal heart rate accelerations with movement; two had breathing movements for more than 20% of the observed time and both had satisfactory perinatal outcomes; the other three had poor perinatal outcomes and had either prolonged apnea or fetal breathing for less than 10% of the observed time. Therefore, the combination of a positive OCT with a reduced incidence of fetal breathing gave a poor prognosis while in this small group of patients fetal breathing for more than 20% of the time indicated a healthy fetus despite a positive OCT.

Manning and colleagues[54] similarly combined nonstress antenatal cardiotocography with fetal breathing to assess predictive accuracy. They found that if both cardiotocography and fetal breathing were abnormal then 45% of fetuses had low Apgar scores at birth. McCune[31] failed to find any correlation between patterns of fetal breathing, heart rate, and perinatal outcome. Marsal has postulated that looking at some other quality of fetal breathing rather than the incidence may be of more value.

Van Weering and associates,[34] in a series of small-for-dates fetuses, found that the absence of an increase in fetal breathing with maternal hypercapnia followed by a positive reaction to maternal hyperoxia was a poor prognostic sign. In normal pregnancy they found, in common with Ritchie and Lakhani,[33] that maternal hyperoxia does not influence fetal breathing.

In two studies using fetal breathing alone as the index of fetal health, Manning[57] and Trudinger and associates[28] found a wide range of incidence of fetal breathing in the abnormal pregnancies. Prolonged apnea or a grossly reduced incidence, however, did seem to be of poor prognostic significance. In Manning's study three of four fetuses with prolonged apnea required intubation at birth while in the study of Trudinger and associates three fetuses with an incidence of less than 10% died in the perinatal period. Trudinger and associates had standardized the procedure by giving a 50 gm glucose load to the mothers 30 minutes before screening.

As can be seen from Fig. 4, two patterns of fetal breathing emerge in the small-for-dates group; breathing for a greater or lesser percentage of time than expected. However, there is a considerable degree of overlap and in the individual case the prognostic sig-

nificance of a particular pattern is difficult to assess when fetal breathing is used as the sole parameter of fetal health.

Roberts and associates[30] in their study of the incidence of fetal breathing throughout the day found a low incidence in three asymmetrically growth-retarded fetuses but no such reduction in two symmetrically growth-retarded fetuses. The inference is that a fetus with a reduced hepatic glycogen store is unable to tolerate physical exercise for prolonged periods of time; in other words, the starved fetus is not as physically fit as his well-nourished brother. Table II summarizes published data on the correlation of antenatal fetal breathing with perinatal outcome.

Comment

The pattern that emerges from a review of results so far presented indicates that measurement of fetal breathing may be of value antenatally but the initial hopes that this would provide the answer to difficult perinatal therapeutic problems have not been borne out.

Most benefit would appear to be gained from combining fetal breathing results with some more established method of assessing fetal health such as cardiotocography. The very wide range of normal in the incidence of fetal breathing, which appears to be governed to a certain extent by time of day and maternal blood glucose fluctuation, suggests that standardization of the circumstance of measurement would allow more direct comparison of results.

The study of fetal breathing in labor is in its infancy and basic physiologic research needs to be done before any clinical application can be hoped for. In common with many procedures in obstetrics fetal breathing investigation is undergoing a period of re-evaluation. While the place of fetal breathing in the investigation of fetal physiology and pharmacology is unrivalled, clinical application in the management of patients needs to await further confirmation of its value.

The "purpose" of fetal breathing remains obscure although it has been suggested that movement is necessary for adequate development of the lung. It might also be speculated that, as in the adult, rhythmic movement increases the production of prostacyclin in the pulmonary vasculature. This recently discovered prostaglandin is thought to play an important role as a circulating anti–platelet-aggregatory hormone in the arterial circulation.[58, 59] However, the last word should perhaps be left to Ballantyne[3] who, in 1902, considered fetal breathing to be "thoracic gymnastics in preparation for the great extra-uterine function of atmospheric respiration."

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COMMUNICATIONS IN BRIEF

This section is suitable for reporting results of therapeutic trials, descriptions of new procedures or instruments, and case reports which illustrate a principle. Reports should be limited to seven hundred words and two references. Use of an illustration or table requires a proportionate reduction in total words.

Induction of ovulation and pregnancy in a woman with sex chromosomal mosaicism 45,X/46,XX/47,XXX

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A WOMAN WITH secondary amenorrhea, polycystic ovary disease (POD), and sex chromosomal mosaicism 45,X/46,XX/47,XXX was treated once with human menopausal gonadotropin (hMG) and human chorionic gonadotropin (hCG). She conceived and, in week 30 of gestation, spontaneously gave birth to normal twins, a 46,XY male and a 46,XX female.

B. T., a 32-year-old white woman, para 0000, was first seen in 1965 with a history of incomplete development of secondary sexual characteristics and failure of cyclic menses to occur by age 21. A pelvic examination showed a well-estrogenized vagina, a normal-size uterus, and ovaries estimated to be approximately 2 by 2 cm in size. She was 177 cm in height with an arm span of 181 cm. Buccal and vaginal smears were both positive for nuclear sex chromatin. Eighty-four metaphases from peripheral blood were 46,XX and 14 cells had 45,X karyotype. A repeat karyotpye done 5 years later showed 46,XX in 86 cells, 45,X in 8 cells and 47,XXX in 6 cells.

When treated with Provera orally, in doses of 10 mg/day for 10 days, vaginal bleeding followed in each of three cycles. She was given a course of 100 mg of clomiphene citrate for 8 days without response. Laparoscopy revealed the ovaries to be 2 by 2 cm in size and both fallopian tubes were found to be patent. Biopsies of both ovaries revealed "fibrous tissue" and a minute area of ovarian stroma in which no follicles were identified.

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Her history further revealed that she has seven siblings, two of whom are identical twin girls. Two sisters are dizygotic twins and two brothers are fraternal twins. One sister is married and has produced a healthy child.

The patient married in 1975 and 2 years later wanted to become pregnant. Despite the 45,X/46,XX/47,XXX karyotype and failure to demonstrate oocytes on ovarian biopsy, but based on the low plasma follicle-stimulating hormone (FSH) and withdrawal bleeding following progesterone, it was felt that oocytes were present and induction of ovulation was possible.

The low plasma levels of FSH and slightly elevated levels of lutenizing hormone (LH) and E_2 indicated a polycystic ovary syndrome and clomiphene citrate would be the first choice for induction of ovulation. However, clomiphene citrate had already been tried twice without response. It was therefore decided to induce ovulation with hMG (Pergonal).

The treatment with Pergonal lasted 12 days and the patient was monitored with daily E_2 determinations in plasma. The final dose of Pergonal was 4 ampules/day. Following hCG administration, she ovulated and conceived. On day 69, the uterus was enlarged to the size of an 8 to 10 week pregnancy; 3 days later ultrasound examination revealed the presence of twins.

Except for an episode of vaginal spotting from weeks 14 to 17 of gestation, the prenatal course continued normally until the early part of week 30 when, without difficulty, she was delivered vaginally of twins. Due to the spotting during gestation, she refused amniotic fluid examination.

Twin A, a 46,XY male, weighed 1,350 grams and Twin B, a 46,XX female, weighed 1,560 grams. Both infants appeared phenotypically normal and are doing well postnatally (12 months).

Clinical features in women with sex chromosome mosaicism involving a 45,X cell line are more variable than in those women with a single 45,X cell line. Somatic defects may be absent or milder, or may be indistinguishable from those of a typical Turner's phenotype. Gonadal development seen in sex chromosomal mosaicism may range from nonfunctioning streak ovaries to normal ovaries capable of producing regular menses

and spontaneous ovulation. The variation may be explained by the proportion of primordial germ cells which bear a 45,X karyotype to those with a 46,XX or 47,XXX constitution.

Our patient had a positive buccal smear and high proportion of primordial germ cells of 46,X karyotype compared to those with 45,X and demonstrated very few minor somatic features of Turner's syndrome. She represents a select group of women who may seek evaluation of infertility. Ordinarily, a woman with secondary amenorrhea and almost complete secondary sex development might not be examined for sex chromosomal abnormality.

Reyes, Koh, and Faiman[1] reviewed the literature up to 1976 regarding fertile women with a 45,X mosaicism. They reported on 25 women who had been pregnant 58 times. Eight of these women had cell lines similar to that of the patient reported in this study. Their history included eight abortions, two malformed stillborn infants, and 12 live births with one set of twins.

The 45,X line is generally conceded to be a postfertilization phenomenon arising by nondysjunction at or after the first cleavage. The etiologic agent responsible for nondysjunction in these situations is unknown, but twinning among siblings has been noted to be associated. Thus, Nance and Uchida[2] reported seven sets of monozygotic twins in 34 siblings in whom the proband was apparently 45,X.

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Benign blue nevus of the uterine cervix

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Recently we encountered a case of blue nevus of the uterine cervix. Review of the literature revealed only 17 previously reported cases. Clinically, the lesion has sometimes been mistaken for malignant melanoma. Clinicians should therefore be aware of this lesion.

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A 72-year-old black woman was admitted to Grady Memorial Hospital for subtrochanteric fracture of the right femur. Pathologic examination of the bone showed the structure of an anaplastic carcinoma. Since the patient had a pelvic mass and a pathologic fracture, she was referred to the Gynecologic Tumor Service, although she had no gynecologic symptoms. Physical examination showed a midline pelvic mass extending above the umbilicus but not related to the uterine cervix or adnexa. The parametrium was uninvolved. The cervix demonstrated a smooth mucosal surface on which a spherical blue lesion, 0.4 cm in diameter, was seen at the 11 o'clock position. The lesion was biopsied and at the same time biopsies of the cervix, endocervix, and endometrium were obtained. Pathologic examination of the endometrium showed the structure of a mixed mesodermal tumor. The blue lesion of the cervix was composed of subepithelial deposition of heavily pigmented spindle-shaped cells demonstrating long, thin, bipolar cytoplasmic processes. The pigment displayed the characteristic histochemical reaction of melanin and did not stain with Prussian blue stain for iron. No pigment was present in the overlying cervical epithelium. The histological findings were diagnostic of a blue nevus (Fig. 1). The patient's lesion was diagnosed as Stage IVB mixed mesodermal tumor of the uterine corpus. She died very soon after the diagnosis was made.

There have been 17 previously reported cases of the blue nevus arising in the uterine cervix, and two cases arising in the vagina.[1, 2] The majority of them are small and detected as an incidental finding on clinical or pathologic examination. Occasionally a blue nevus can be very large. Tobon and Murphy[1] described a blue nevus located at the apex of the anterior vaginal wall of a 73-year-old woman. The nevus measured 1.0 cm in diameter and was clinically diagnosed as melanoma. Rodriguez and Ackerman[2] described the case of a 19-year-old woman with a large, cellular blue nevus involving the cervix, vagina, and hymenal ring. The lesion was discovered during the routine prenatal care in the fifth month of pregnancy. The tumor in the vagina was hard and nodular. The pelvic examination was unremarkable. No lymphadenopathy was detected. The patient was lost to follow-up after 45 months. In a series of 45 cases of cellular blue nevi reported by these authors,[2] three cases were clinically diagnosed as malignant melanoma. An erroneous clinical and pathologic diagnosis of malignant melanoma in one patient resulted in unwarranted radical surgery. It is very important therefore that both clinicians and pathologists should be familiar with the gross and microscopic appearance of a cellular blue nevus. Although instances of malignant blue nevi or blue nevi metastasizing in the regional lymph nodes are reported in the literature, all the 17 cases of cervical blue nevi had a benign course. Adequate local exicision is, therefore, the treatment of choice. Incomplete excision can result in recurrence.

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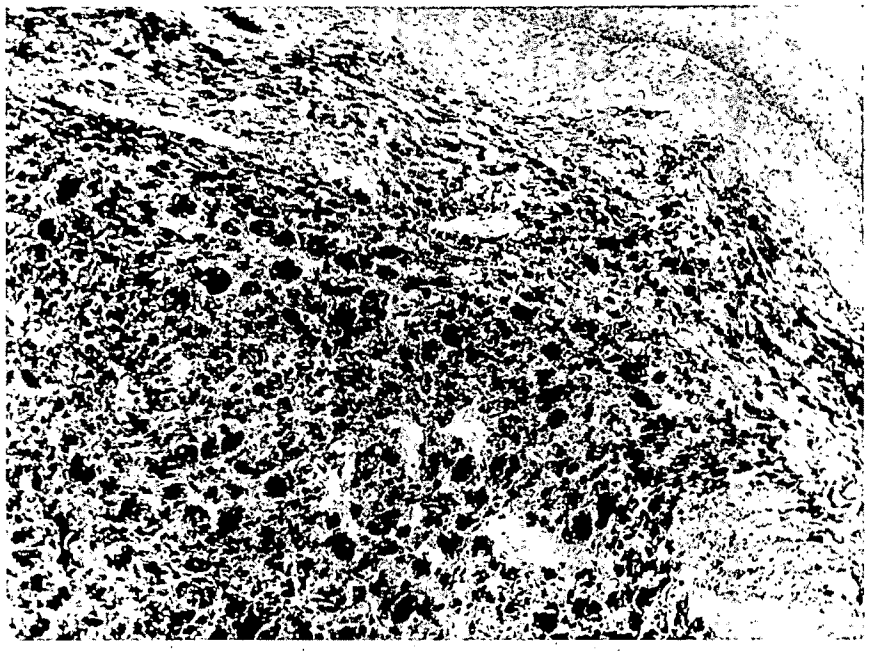


Fig. 1. Section of the cervix showing subepithelial deposition of heavily pigmented bundles of melanocytic cells. Note clear space between blue nevus and normal cervical mucosa. (Hematoxylin and ecsin; ×78.)

Besides blue nevi, one occasionally encounters melanosis or melanoma primarily involving the vagina or the uterine cervix. This phenomenon is histogenetically interesting. It is a generally held opinion that Schwann cells transforming into melanocytes are responsible for such a pigment disorder. This view is disputed by others and the precise mechanism is not known.

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Correction of postpartum uterine inversion by the application of intravaginal hydrostatic pressure

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ACUTE INVERSION of the postpartum uterus is fortunately rare, occurring in approximately 1 out of 20,000 pregnancies. Few obstetric emergencies are more demanding of immediate intervention than this condition. Most methods described for the management of acute postpartum uterine inversion require digital replacement. In 1945, O'Sullivan[1] reported on a simple and effective method of dealing with this condition. His technique involved the occlusion of the vaginal introitus with the forearm, while a warm antiseptic solution was introduced, under pressure, into the vagina from a douche can held about 3 feet above the level of the patient's perineum. The purpose of this manuscript is to report on the satisfactory application of a modified O'Sullivan technique in two cases of acute postpartum uterine inversion.

The inverted uterine fundus is gently replaced into the vagina and a douche nozzle is directed into the posterior fornix. An antiseptic solution is liberally applied to the surgeon's cleansed forearm, which is then forcefully applied to the vaginal introitus longitudinally, while an assistant presses the labia to the surgeon's forearm so as to completely occlude the vaginal orifice. A second assistant forces 2 to 3 L of a warm, sterile saline solution through the douche nozzle under pressure into the vagina. The pressure is maintained for approximately 5 minutes, whereupon the surgeon removes his forearm and the saline is allowed to gush from the vagina. A vaginal examination is then performed in order to evaluate the effect of management. The procedure can be repeated if necessary.

M. V., an obese 29-year-old woman, had an uneventful prenatal course followed by a spontaneous vaginal delivery at

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term. An attempt to deliver her placenta by guided cord traction (the Brandt-Andrews method[2]) resulted in complete inversion of the uterus. An intravenous line was introduced and blood was immediately cross-matched. Thereupon, the placenta was detached without difficulty and the uterus was gently reduced into the vagina. The modified O'Sullivan technique as described above was employed and the uterus reverted to its normal anatomic position within 5 minutes of initiating the procedure. Shock did not ensue and the total estimated volume of blood loss was 450 ml. The patient tolerated the procedure well and prophylactic antibiotics were prescribed. She made an uneventful recovery.

B. G., a slender 27-year-old non-Caucasian multiparous patient, had a benign prenatal course followed by a spontaneous delivery at term. It became evident after 45 minutes in the third stage of labor that despite the infusion of oxytocics, the placenta by the Credé method. This was followed by incomplete uterine inversion, with the fundus of the uterus protruding through the cervix, but not through the vaginal introitus. The placenta was easily detached from the uterine fundus, whereupon the modified O'Sullivan method was used to correct the inversion. This was achieved within 5 minutes of initiating the procedure. The patient did not become shocked and made an uneventful recovery.

The conventional method for managing acute postpartum uterine inversion is digital replacement; where this fails, a laparotomy is performed and surgical correction achieved. Profound vasovagal and hemorrhagic shock often accompanies this condition. Digital manipulation of the inverted uterine body is likely to aggravate both the vasovagal and hemorrhagic components of shock.

It is important to bare in mind that postpartum uterine inversion is often associated with a firmly attached placenta (i.e., accreta, increta, and percreta). An attempt to detach such a placenta piecemeal will result in uncontrollable hemorrhage. Accordingly, it is advisable to correct the inversion without prior removal of the placenta in such cases. Once this has been achieved, manual removal of the placenta can be attempted under general anesthesia, and in full preparation for hysterectomy should bleeding become uncontrollable.

The O'Sullivan technique as described above has several advantages: (1) it can be performed without general anesthesia; (2) the fluid, introduced under pressure into the vagina, exerts hydraulic pressure on the inverted uterus in a manner which allows the most efficient reduction of the inverted organ; (3) the method precludes the requirement for digital manipulation of the inverted uterus and thereby reduces the risk of aggravating the shock; (4) the method is both simple and reliable.

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Methergine-induced uterine tetany treated with epinephrine: Case report

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UNCONTROLLABLE uterine tetany leading to fetal damage can result from the inappropriate use of oxytocic agents. Fig. 1 shows the direct fetal monitor tracing of a patient who inadvertently received intramuscular methergine while in labor. The effects of methergine and the subsequent therapy with epinephrine are documented.

An 18-year-old white woman, gravida 1 para 0, was seen regularly for prenatal care. The patient was admitted for induction of labor at 43 weeks, following an abnormal nonstress test. AROM was performed at 0930 hours with application of a scalp electrode and intrauterine catheter. The patient entered labor without oxytocic stimulation. At 1650, the patient was inadvertently given 0.2 mg of methergine intramuscularly, ordered for another patient who had recently been delivered. At 1700, the cervix was 80% effaced and 2 to 3 cm dilated. At 1710, the strip chart showed contractions of increasing frequency and hypertonus. The fetal heart rate (FHR) had decreased to 80 to 90 bpm with increased variability. Then ½ cc of 1:1000 epinephrine was given rapidly intravenously. There was a rapid decline in the excessive uterine activity. Concomitantly, a fall in the FHR to 40 to 50 bpm with a flat baseline occurred, with a subsequent slow return to baseline. Hypertonus gradually recurred and another injection of epinephrine (⅙ cc of 1:1000) was given intravenously. A similar FHR-UC response was seen, but was of shorter duration. Uterine activity gradually resumed a normal labor pattern and the patient was delivered of a 6 lb ¼ oz male infant, with Apgar scores of 5/7, by low forceps 6 hours later. Moderately severe variable decelerations occurred during the second stage and may have contributed to the depressed 1 minute Apgar score. The baby did well and was discharged to his home with the mother on the third postpartum day. Subsequent infant examinations over 9 months have been normal.

The dramatic effects of oxytocic agents on both uterine activity and FHR are illustrated by this case. Methergine is an ergot derivative that causes an irregular polysystole which can progress to tetany.[1] It was widely studied as a labor-inducing agent in the 1940's but, due to difficulty in regulating dosage and occurrence of hypertonus, its use was discontinued.

The opinions or assertions contained herein are those of the authors and are not to be construed as official or reflecting the views of the Department of the Navy or the Department of Defense.

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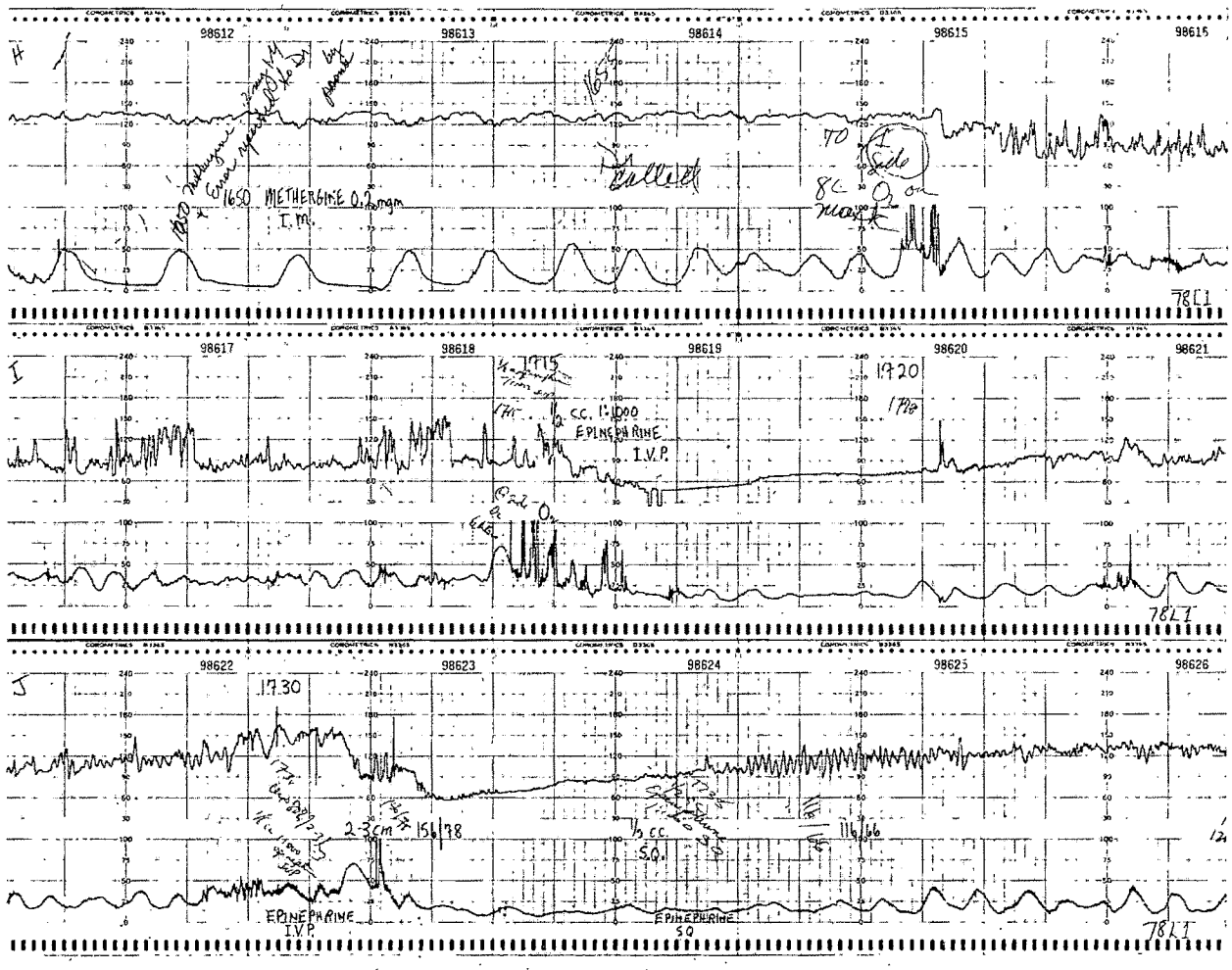


Fig. 1. The FHR-UC characteristics with the use of direct methods for monitoring are shown. The dramatic response associated with epinephrine administration is evident.

Epinephrine is known to produce uterine relaxation, but of such short duration that it is generally not considered useful when prolonged relaxation is required.[1] It has also been found to cause bradycardias in the human fetus, although true distress from its administration has not been documented.[2]

In situations of uterine tetany secondary to an oxytocic infusion, therapy is simply to discontinue the offending drug.

The therapy of iatrogenic tetany secondary to drugs given in an unregulated manner is unclear. In the face of such a crisis situation, the decision in this case was made to utilize epinephrine, which is known to have tocolytic action. Examination of the tracing reveals the two effects. The prompt uterine relaxation represents the β-sympathomimetic effect of the drug. The profound, fetal bradycardia is probably due to an α-adrenergic effect on the uterine vasculature with resultant decreased uterine blood flow. A direct effect on the fetal circulation and myocardium cannot be ruled out, but seems unlikely in the face of uterine hypertonus.[2]

The use of epinephrine in this patient may have been beneficial to the fetus. Epinephrine clearly reduced uterine activity following both episodes of intravenous administration. Even though the second dose was reduced by two thirds, an equivalent tocolytic effect occurred. The FHR response suggests a stress factor which likely was related to vasoconstriction. The FHR response following the second dose was less dramatic, suggesting a dose-related response.

In cases of excessive uterine activity, it would be desirable to achieve tocolysis without an adverse effect on uterine blood flow. β-Sympathomimetic drugs possess such activity but are unavailable in this country. Epinephrine in low dosage might achieve a primary beta effect, but titration would be difficult.

In view of this case, it would appear that another alternative agent, such as magnesium sulfate, should be considered.

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Zavoshy, John J., 14081 Pike Rd., Saratoga, California 95070

International Conference of Biological Engineering Society: Foetal and Neonatal Physiological Measurements

The International Conference of the Biological Engineering Society, "Foetal and Neonatal Physiological Measurements," will be held September 3-5, 1979, in Oxford, England.

Offers of papers should be made now and submitted with an abstract on one side of A4 paper to the Programme Chairman: Dr. P. Rolfe, Bioengineering Unit, Department of Paediatrics, John Radcliffe Hospital, University of Oxford, Headington, England 0X3 9DU.

All other enquiries and requests for further information should be directed to: Keith Copeland, Honorary Secretary, Biological Engineering Society, c/o Royal College of Surgeons of England, 35/43 Lincoln's Inn Fields, London, England WC2A 3PN.

Professor K. de Snoo Memorial Congress

The Professor K. de Snoo Memorial Congress, in cooperation with the Eleventh Meeting of the Organisation Gestosis, will be held at The Hague, The Netherlands, September 18-21, 1979.

For information write: The Secretariat, P. O. Box 175, 2770 AD Boskoop, The Netherlands.

Second Trimester Abortion: Perspectives After a Decade of Experience

"Second Trimester Abortion: Perspectives After a Decade of Experience" sponsored by the Department of Obstetrics and Gynecology, University of North Carolina at Chapel Hill, and The Charles A. Fields Foundation, Ltd., Madison Wisconsin, will be presented in Chapel Hill, North Carolina, at the Carolina Inn, September 27-28, 1979.

For information write: The University of North Carolina, c/o Office of Continuing Education, University NC School of Medicine, 236 MacNider Bldg. 202H, Chapel Hill, North Carolina 27514.

Nutrition and the Killer Diseases

The Institute of Human Nutrition at Columbia University is sponsoring a 2 day symposium, "Nutrition and the Killer Diseases," at the Sheraton Centre (formerly Americana Hotel), 52nd St. and Seventh Ave., New York, New York, November 29-30, 1979.

For further information write: Director, Institute of Human Nutrition, Columbia University, 701 W. 168th St., New York, New York 10032.

Interdisciplinary Aspects in Diseases of the Female Breast

An International Congress on Seniology: Interdisciplinary Aspects in Diseases of the Female Breast, organized by the Senologic International Society, will be held in Hamburg, Germany, May 27-31, 1980.

Direct inquiries to: Prof. Dr. H.-J. Frischbier, Universitäts Frauenklinik, Martinistrasse 52, 2000 Hamburg 20, Germany.

Annual autumn seminar of the Department of Obstetrics and Gynecology, University of Minnesota Medical School

The Department of Obstetrics and Gynecology of the University of Minnesota Medical School will present its annual autumn seminar, October 24-26, 1979, at the IDS Center Conference Theatre in Minneapolis, Minnesota.

For further information contact: Office of Continuing Medical Education, Box 293 Mayo Memorial Bldg., 420 Delaware St. S.E., Minneapolis, Minnesota 55455.

Office Ultrasound

The University of Tennessee Center for the Health Sciences, Knoxville, Tennessee, will present "Office Ultrasound," October 25, 26, 27, 1979, at the Sheraton Inn, Gatlinburg, Tennessee.

For further information contact: Department of Continuing Medical Education, U.T.C.H.S./K.U., Drawer 116, 1924 Alcoa Highway, Knoxville, Tennessee 37920. Phone: (615)971-3345.

International Congress on Ageing and Gonadal Function: Biological and Clinical Aspects in Male and Female

An International Congress on Ageing and Gonadal Function: Biological and Clinical Aspects in Male and Female, sponsored by the Italian Society of Obstetrics and Gynecology, Italian Society of Andrology and Fondazione Giovanni Lorenzini, will be held in Rome on November 28-30, 1979.

A limited number of communications (in the form of posters and talks) will be considered by the Scientific Committee.

For further information please contact the Organizing Secretariat: Fondazione Giovanni Lorenzini, via Monte Napoleone, 23-20121 Milan, Italy. Telephone: (02) 783.868 or 702.267. Cable: LORENZFOUND.

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BELLERGAL-S™ TABLETS

Composition: Each Bellergal-S Tablet contains: phenobarbital, USP, central sedative (Warning: May be habit forming), 40.0 mg; Gynergen (ergotamine tartrate, USP) sympathetic inhibitor, 0.6 mg; Bellafoline (levorotatory alkaloids of belladonna, as malates) parasympathetic inhibitor, 0.2 mg.

Properties and Therapeutics: Based on the concept that functional disorders frequently involve hyperactivity of both the sympathetic and parasympathetic nervous systems, the ingredients in Bellergal are combined to provide a balanced preparation designed to correct imbalance of the autonomic nervous system. The integrated action of Bellergal is effected through the combined administration of ergotamine and the levorotatory alkaloids of belladonna, specific inhibitors of the sympathetic and parasympathetic respectively, reinforced by the synergistic action of phenobarbital in dampening the cortical centers.

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Interval treatment of *recurrent, throbbing headache*.

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Precautions: Even though the ergotamine tartrate content of this product is extremely low and untoward effects have been rare and insignificant, caution should be exercised if large or prolonged dosage is contemplated, and physicians should be alert to possible peripheral vascular complications in patients highly sensitive to ergot. Due to presence of a barbiturate, may be habit forming.

Side Effects: Blurred vision, dry mouth, flushing, drowsiness occur rarely.

Dosage: Bellergal-S Tablets: One in the morning and one in the evening.

How Supplied: Bellergal-S Tablets (compressed, scored tablets of tricolored pattern: dark green, orange and light lemon yellow) in bottles of 100.

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NONHORMONAL therapy for menopausal vasomotor instability is receiving renewed attention.

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So when estrogen therapy is undesirable... prescribe Bellergal-S Tablets.

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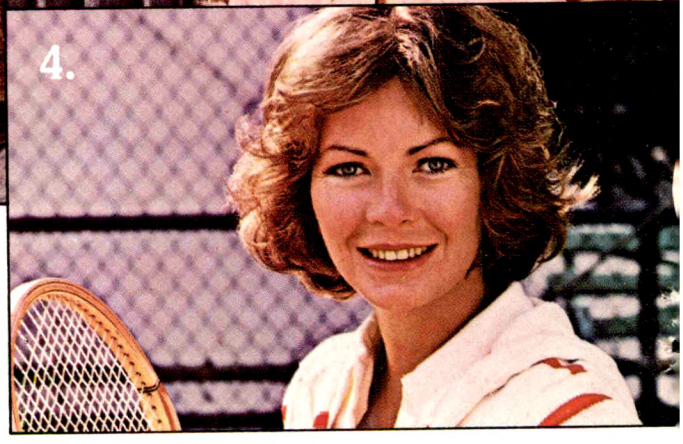
Why the choice is Cu-7®

intrauterine copper contraceptive









1. She wants nonhormonal contraception.
2. She wants to space her family.
3. She smokes.
4. She has passed the "Pill" years.

Freedom—intrauterine contraception is the most convenient of all contraceptive methods.

Comfort—smallest inserter diameter of all IUDs. This means minimal discomfort during insertion.

Cu-7	Lippes Loop® D	Saf-T-Coil® (Nullip)	Saf-T-Coil® (Standard)
3.07 mm.	5.33 mm.	3.76 mm.	4.50 mm.

Security—high efficacy and relatively low incidence of expulsion and medical removal.

(Rates—based on labeling claims—expressed as events per 100 women through 12 months of use for parous women)*	Cu-7[1]	Lippes Loop® D[2]	Saf-T-Coil[2]
Pregnancy	1.9	2.7	2.4
Expulsion	5.7	12.7	18.3
Medical Removal	10.9	15.2	15.6

*These rates are derived from separate studies conducted by different investigators in several population groups. Different rates have been reported from other clinical trials.

References: 1. Data on file at Searle Laboratories. 2. Physicians' Desk Reference, Medical Economics Company, Oradell, N.J., 1978, pp. 1216, 1521.

Intrauterine contraception is not appropriate for all women. Please see complete product information prior to use. A brief summary of product information appears on the next page.

Description: The plastic component of the Cu-7 is composed of pharmaceutical grade polypropylene homopolymer with barium sulfate added to render it radiopaque. Its shape approximates the number 7. It is substantially smaller than previously available intrauterine devices; the vertical dimension measures 36 mm. and the horizontal, 26 mm.

Coiled around the vertical limb is a pure, virgin electrolytic copper wire providing approximately 200mm² of exposed copper surface area. A retrieval thread is fastened to the free end of the vertical limb of the Cu-7.

The Cu-7 is supplied with a simple tubular polypropylene inserter. All components are sterile.

Mode of Action: Available data indicate that the contraceptive effectiveness of the Cu-7 is enhanced by a minute quantity of copper released continuously from the coiled copper into the uterine cavity.

The exact mechanism by which metallic copper enhances the contraceptive effect of an IUD has not been conclusively demonstrated. Various hypotheses have been advanced, the most common being that copper placed in the uterus interferes with enzymatic or other processes that regulate blastocyst implantation.

Animal studies suggest that copper may play an additional role by reduction of sperm transport within the uterine environment.

Indication and Usage: The Cu-7 is indicated for contraception.

Contraindications: The Cu-7 should not be inserted when any of the following conditions exist: pregnancy or suspicion of pregnancy; abnormalities of the uterus resulting in distortion of the uterine cavity; acute pelvic inflammatory disease or a history of repeated pelvic inflammatory disease; postpartum endometritis or infected abortion in the past three months; known or suspected uterine or cervical disease such as hyperplasia or carcinoma including unresolved, abnormal "Pap" smear; vaginal bleeding of unknown etiology; untreated acute cervicitis until infection is controlled; diagnosed Wilson's disease; known or suspected allergy to copper; previous ectopic pregnancy, and significant anemia.

Warnings

1. Pregnancy: (a) Long-term effects. The long-term effects on the offspring of the presence of copper in the uterus when pregnancy occurs with the Cu-7 are unknown.

(b) Septic abortion. Reports have indicated an increased incidence of septic abortion associated in some instances with septicemia, septic shock and death in patients becoming pregnant with an IUD in place. Most of these reports have been associated with the mid-trimester of pregnancy. In some cases, the initial symptoms have been insidious and not easily recognized. If pregnancy should occur with a Cu-7 in situ, the Cu-7 should be removed if the thread is visible or, if removal proves to be or would be difficult, interruption of the pregnancy should be considered and offered to the patient as an option, bearing in mind that the risks associated with an elective abortion increase with gestational age.

(c) Continuation of pregnancy. If the patient chooses to continue the pregnancy and the Cu-7 remains in situ, she must be warned of the increased risk of spontaneous abortion and the increased risk of sepsis, including death. The patient must be closely observed and she must be advised to report immediately all abnormal symptoms, such as flu-like syndrome, fever, abdominal cramping and pain, bleeding, or vaginal discharge, because generalized symptoms of septicemia may be insidious.

2. Ectopic pregnancy: (a) A pregnancy which occurs with an IUD in situ is more likely to be ectopic than a pregnancy occurring without an IUD. Therefore, patients who become pregnant while using a Cu-7 should be carefully evaluated for the possibility of an ectopic pregnancy.

(b) Special attention should be directed to patients with delayed menses, slight metrorrhagia and/or unilateral pelvic pain, and to those patients who wish to interrupt a pregnancy occurring in the presence of a Cu-7, to determine whether ectopic pregnancy has occurred.

3. Pelvic infection. An increased risk of pelvic inflammatory disease associated with the use of IUDs has been reported. While unconfirmed, this risk appears to be greatest for young women who are nulliparous and/or who have a multiplicity of sexual partners. Salpingitis can result in tubal damage and occlusion, thereby threatening future fertility. Therefore, it is recommended that patients be taught to look for symptoms of pelvic inflammatory disease. The decision to use an IUD in a particular case must be made by the physician and patient with the consideration of a possible deleterious effect on future fertility.

Pelvic infection may occur with a Cu-7 in situ and at times result in the development of tubo-ovarian abscesses or general peritonitis. The symptoms of pelvic infection include: new development of menstrual disorders (prolonged or heavy bleeding), abnormal vaginal discharge, abdominal or pelvic pain, dyspareunia, fever. The symptoms are especially significant if they occur following the first two or three cycles after insertion. Appropriate aerobic and anaerobic bacteriologic studies should be done and antibiotic therapy initiated promptly. If the infection does not show marked clinical improvement within 24 to 48 hours, the Cu-7 should be removed and the continuing treatment reassessed on the basis of the results of culture and sensitivity tests.

4. Embedment: Partial penetration or lodging of the Cu-7 in the endometrium or myometrium can result in a difficult removal. This may occur more frequently in smaller uteri. (See removal instructions.)

5. Perforation. Partial or total perforation of the uterine wall or cervix may occur with the use of the Cu-7, usually during insertions into patients sooner than two months after abortion or delivery or in uterine cavities too small for the Cu-7. The possibility of perforation must be kept in mind during insertion and at the time of any subsequent examination. If perforation occurs, laparotomy or laparoscopy should be performed as soon as medically feasible and the Cu-7 removed. Abdominal adhesions, intestinal penetration, intestinal obstruction, and local inflammatory reaction with abscess formation and erosion of adjacent viscera may result if the Cu-7 is left in the peritoneal cavity.

6. Medical diathermy: The use of medical diathermy (short-wave and microwave) in a patient with a metal-containing IUD may cause heat injury to the surrounding tissue. Therefore, medical diathermy to the abdominal and sacral areas should not be used on patients using a Cu-7.

7. Effects of copper. Additional amounts of copper available to the body from the Cu-7 may precipitate symptoms in women with undiagnosed Wilson's disease. The incidence of Wilson's disease is 1 in 200,000.

Precautions

1. Patient counseling. Prior to the insertion the physician, nurse, or other trained health professional must provide the patient with the Patient Brochure. The patient should be given the opportunity to read the brochure and discuss fully any questions she may have concerning the Cu-7 as well as other methods of contraception.

2. Patient evaluation and clinical considerations. a) A complete medical history should be obtained to determine conditions that might influence the selection of an IUD. A physical examination should include a pelvic examination, "Pap" smear, gonorrhea culture and, if indicated, appropriate tests for other forms of venereal disease. The physician should determine that the patient is not pregnant.

(b) The uterus should be carefully sounded prior to the insertion to determine the degree of patency of the endocervical canal and the internal os, and the direction and depth of the uterine cavity. Exercise care to avoid perforation with the sound. DO NOT USE THE Cu-7 INSERTION INSTRUMENT AS A SOUND. In occasional cases, severe cervical stenosis may be encountered. Do not use excessive force to overcome this resistance.

(c) The uterus usually sounds to a depth of 6 to 8 cm. Insertion of a Cu-7 into a uterine cavity measuring less than 6.5 cm. by sounding may increase the incidence of pain, bleeding, partial or complete expulsion, perforation, and possibly pregnancy.

(d) To reduce the possibility of insertion in the presence of an existing undetermined pregnancy, the optimal time for insertion is the latter part of the menstrual flow or one or two days thereafter. The Cu-7 should not be inserted post partum or post abortion until involution of the uterus is complete. The incidence of perforation and expulsion is greater if involution is not complete.

It is, however, necessary to place the Cu-7 as high as possible within the uterine cavity to help avoid partial or complete expulsion that could result in pregnancy.

Since the Cu-7 represents a different design in intrauterine contraception, physicians are cautioned that it is imperative for them to become thoroughly familiar with the instructions for use before attempting placement of the Cu-7.

(e) IUDs should be used with caution in those patients who have an anemia or a history of menorrhagia or hypermenorrhea. Patients experiencing menorrhagia and/or metrorrhagia following IUD insertion may be at risk for the development of hypochromic microcytic anemia. Also, IUDs should be used with caution in patients receiving anticoagulants or having a coagulopathy.

(f) Syncope, bradycardia or other neurovascular episodes may occur during insertion or removal of IUDs, especially in patients with a previous disposition to these conditions.

(g) Patients with valvular or congenital heart disease are more prone to develop subacute bacterial endocarditis than patients who do not have valvular or congenital heart disease. Use of an IUD in these patients may represent a potential source of septic emboli.

(h) Use of an IUD in those patients with acute cervicitis should be postponed until proper treatment has cleared up the infection.

(i) Since the Cu-7 may be partially or completely expelled, patients should be reexamined and evaluated shortly after the first postinsertion menses, but definitely within three months after insertion. Thereafter annual examination with appropriate medical and laboratory evaluation should be carried out. The Cu-7 should be replaced every three years.

(j) The patient should be told that some bleeding or cramps may occur during the first few weeks after insertion, but if these symptoms continue or are severe she should report them to her physician. She should be instructed on how to check after each menstrual period to make certain that the thread still protrudes from the cervix and cautioned that there is no contraceptive protection if the Cu-7 has been expelled. She should also be cautioned not to dislodge the Cu-7 by pulling on the thread. If a partial expulsion occurs, removal is indicated and a new Cu-7 may be inserted. The patient should be told to return within three years for removal of the Cu-7 and for replacement if desired.

(k) A copper-induced urticarial allergic skin reaction may develop in women using a copper-containing IUD. If symptoms of such an allergic response occur, the patient should be instructed to tell the consulting physician that a copper-containing device is being used.

(l) The Cu-7 should be removed for the following medical reasons: menorrhagia and/or metrorrhagia producing significant anemia; uncontrolled pelvic infection; intractable pain often aggravated by intercourse, dyspareunia; pregnancy, if the thread is visible; endometrial or cervical malignancy; uterine or cervical perforation; or any indication of partial expulsion.

(m) If the retrieval thread cannot be visualized it may have retracted into the uterus or have been broken off, or the Cu-7 may have been expelled. Localization usually may be made by feeling with a probe; if not, x-ray or sonography can be used. When the physician elects to recover a Cu-7 with the thread not visible, the removal instructions should be considered.

(n) If any patient with a Cu-7 suddenly develops overt clinical hepatitis or abnormal liver function tests, appropriate diagnostic procedures should be initiated.

Adverse Reactions: Perforations of uterus and cervix have occurred. Perforation into the abdomen has been followed by abdominal adhesions, intestinal penetration, intestinal obstruction, local inflammatory reaction with abscess formation and erosion of adjacent viscera. Pregnancy has occurred with the Cu-7 in situ and when the Cu-7 has been partially or completely expelled.

The incidence of spontaneous abortion, when conception occurs with intrauterine devices in situ, appears to be increased over that in unprotected women. Insertion cramping, usually of no more than a few seconds duration, may occur; however, some women may experience residual cramping for several hours or even days. Intermenstrual spotting or bleeding or prolonged or increased menstrual flow may occur.

Pelvic infection including salpingitis with tubal damage or occlusion has been reported. This may result in future infertility. Complete or partial expulsion of the Cu-7 may sometimes occur, particularly in those patients with uteri measuring less than 6.5 cm. by sounding. Urticarial allergic skin reaction may occur. The following complaints have also been reported with IUDs although their relation to the Cu-7 has not been established: amenorrhea or delayed menses, backaches, cervical erosion, cystic masses in the pelvis, vaginitis, leg pain or soreness, weight loss or gain, nervousness, dyspareunia, cystitis, endometritis, septic abortion, septicemia, leukorrhea, ectopic pregnancy, difficult removal, uterine embedment, anemia, pain, neurovascular episodes including bradycardia and syncope secondary to insertion, dysmenorrhea, and fragmentation of the IUD.

Directions for Use: The Cu-7 is to be placed within the uterine cavity. See the Procedure for Insertion for two insertion techniques.

The small diameter of the Cu-7 facilitates easy insertion in nulligravidous and nulliparous, as well as parous women. The optimal time of insertion is during the latter part of the menstrual flow or one or two days thereafter. The cervical canal is relatively more patent at this time, and there is little chance that the patient may be pregnant.

Present information indicates that efficacy is retained for 36 months. There is no evidence that contraceptive efficacy decreases with time up to three years of use, but until adequate data indicating a longer effective life become available, the Cu-7 must be removed within 36 months from the date of insertion and a new one inserted if desired. If partial expulsion occurs, removal is indicated, and a new Cu-7 may be inserted. Removal of the Cu-7 may also be indicated in the event of heavy or persistent bleeding.

The physician should become thoroughly familiar with the instructions for use before attempting insertion or removal of the Cu-7.

Clinical Efficacy: In clinical trials of the Cu-7 conducted by Searle Laboratories, use effectiveness was determined as follows for parous and nulliparous women, as tabulated by the life table method. (Rates are expressed as cumulative events per 100 women through 12, 24, and 36 months of use.)

This experience encompasses 387,131 woman-months of use, including 12 months for 11,51 women, 24 months for 7,895, and 36 months for 3,661.

	12 Months		24 Months		36 Months	
	Parous	Nulliparous	Parous	Nulliparous	Parous	Nulliparou
Pregnancy	1.9	1.7	2.9	2.6	3.4	3.4

How Supplied

Available in cartons of 6, 30 and 100 sterile units (Cu-7 with an inserter) and sufficient patient leaflet and identification cards.

Please see complete product labeling for additional information, including insertion and removal instructions.

SEARLE **Searle Laboratories**
Division of Searle Pharmaceuticals Inc.
Box 5110, Chicago, Illinois 60680

Cu-7® intrauterine copper contraceptive

—the leading IUD

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In spite of a 40% reduction in the dose of estrogen, efficacy of Loestrin 1.5/30 is considered comparable to that of combination oral contraceptives containing higher levels of estrogen.
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And if you're concerned about your patients' intake of estrogen over an extended period of time, Loestrin 1.5/30 contains 30 mcg of ethinyl estradiol, so patient exposure to estrogen is reduced.
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a 30-mcg alternative to higher estrogen
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See opposite page for prescribing information.

Brief Summary of Prescribing Information
LOESTRIN® 1.5/30
(1.5 mg norethindrone acetate and 30 mcg ethinyl estradiol tablets, USP) See section under Special Notes on Administration and How Supplied.

DESCRIPTION
Loestrin 1.5/30 Products are progestogen-estrogen combinations.

INDICATION AND USAGE
Loestrin 1.5/30 Products are indicated for the prevention of pregnancy in women who elect to use oral contraceptives.

In clinical trials with Loestrin 1.5/30 involving 17,139 therapy cycles, there was a pregnancy rate of 0.49 per 100 woman years.

Dose-related risk of thromboembolism from oral contraceptives: Studies have shown a positive association between the dose of estrogens in oral contraceptives and the risk of thromboembolism. It is prudent and in keeping with good principles of therapeutics to minimize exposure to estrogen. The oral contraceptive prescribed for any given patient should be that product which contains the least amount of estrogen that is compatible with an acceptable pregnancy rate and patient acceptance.

CONTRAINDICATIONS
1. Thrombophlebitis or thromboembolic disorders
2. A past history of deep-vein thrombophlebitis or thromboembolic disorders
3. Cerebral vascular or coronary artery disease
4. Known or suspected carcinoma of the breast
5. Known or suspected estrogen-dependent neoplasia
6. Undiagnosed abnormal genital bleeding
7. Known or suspected pregnancy (See No. 5 under WARNINGS.)

WARNINGS

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

The use of oral contraceptives is associated with increased risk of several serious conditions including thromboembolism, stroke, myocardial infarction, hepatic adenoma, gallbladder disease, and hypertension. Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks.

1. *Thromboembolic Disorders and Other Vascular Problems:* An increased risk of thromboembolic and thrombotic disease associated with the use of oral contraceptives is well-established. Studies have demonstrated an increased risk of fatal and nonfatal venous thromboembolism and stroke, both hemorrhagic and thrombotic.

Cerebrovascular disorders: In a collaborative study in women with and without predisposing causes, it was estimated that the risk of hemorrhagic stroke was 2.0 times greater in users than nonusers, and the risk of thrombotic stroke was 4.0 to 9.5 times greater.

Myocardial infarction: An increased risk of myocardial infarction associated with oral contraceptives has been reported confirming a previously suspected association. These studies found that the greater the number of underlying risk factors (cigarette smoking, hypertension, hypercholesterolemia, obesity, diabetes, history of preeclamptic toxemia) for coronary artery disease, the higher the risk of developing myocardial infarction, regardless of whether the patient was an oral contraceptive user or not. Oral contraceptives, however, were found to be a clear additional risk factor.

It has been estimated that users who do not smoke (smoking is considered a major predisposing condition to myocardial infarction) are about twice as likely to have a fatal myocardial infarction as nonusers who do not smoke. Oral contraceptive users who are smokers have about a fivefold increased risk of fatal infarction compared to users who do not smoke, but about a tenfold to twelvefold increased risk compared to nonusers who do not smoke. The amount of smoking is also an important factor.

Risk of dose: In an analysis of data, British investigators concluded that the risk of thromboembolism including coronary thrombosis is directly related to the dose of estrogen used in oral contraceptives; however, the quantity of estrogen may not be the sole factor involved.

Estimate of excess mortality from circulatory diseases: The risk of diseases of the circulatory system is concentrated in older women, in those with a long duration of use, and in cigarette smokers.

A study of available data from a variety of sources concluded that the mortality associated with all methods of birth control is low and below that associated with childbirth, with the exception of oral contraceptives in women over 40 who smoke.

The risk of thromboembolic and thrombotic diseases associated with oral contraceptives increases with age after approximately age 30 and, for myocardial infarction, is further increased by hypertension, hypercholesterolemia, obesity, diabetes, or history of preeclamptic toxemia, and especially by cigarette smoking.

The physician and the patient should be alert to the earliest manifestations of thromboembolic and thrombotic disorders. Should any occur or be suspected, the drug should be discontinued immediately.

A fourfold to sixfold increased risk of postsurgery thromboembolic complications has been reported in users. If feasible, oral contraceptives should be discontinued at least four weeks before surgery of a type associated with an increased risk of thromboembolism or prolonged immobilization.

2. *Ocular lesions:* Neuro-ocular lesions, such as optic neuritis or retinal thrombosis, have been associated with the use of oral contraceptives. Discontinue the oral contraceptive if there is unexplained sudden or gradual, partial, or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal vascular lesions.

3. *Carcinoma:* Long-term continuous administration of estrogen in certain animal species increases the frequency of carcinoma of the breast, cervix, vagina, and liver.

In humans, an increased risk of endometrial carcinoma associated with the prolonged use of exogenous estrogen in postmenopausal women has been reported. However, there is no evidence suggesting increased risk of endometrial cancer in users of conventional combination or progestogen-only oral contraceptives.

Studies found no evidence of increase in breast cancer in women taking oral contraceptives; however, an excess risk in users with documented benign breast disease was reported.

There is no confirmed evidence of an increased risk of cancer associated with oral contraceptives. Close clinical surveillance of users is, nevertheless, essential. In cases of undiagnosed persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be taken to rule out malignancy. Women with a strong family history of breast cancer, or who have breast nodules, fibrocystic disease, or abnormal mammograms, should be monitored with particular care.

4. *Hepatic Tumors:* Benign hepatic adenomas have been found to be associated with oral contraceptives. Because hepatic adenomas may rupture and may cause death through intra-abdominal hemorrhage, they should be considered in women presenting abdominal pain and tenderness, abdominal mass, or shock.

A few cases of hepatocellular carcinoma have been reported in women taking oral contraceptives. The relationship of these drugs to this type of malignancy is not known at this time.

5. *Usage in or Immediately Preceding Pregnancy. Birth Defects in Offspring, and Malignancy in Female Offspring:* During early pregnancy, female sex hormones may seriously damage the offspring.

An increased risk of congenital anomalies, including heart defects and limb defects, has been reported with the use of oral contraceptives in pregnancy.

There is some evidence that triploidy and possibly other types of polyploidy are increased among abortuses from women who become pregnant soon after ceasing oral contraceptives.

Pregnancy should be ruled out before continuing an oral contraceptive in any patient who has missed two consecutive menstrual periods. If the patient has not adhered to the schedule, the possibility of pregnancy should be considered at the time of the first missed period, and oral contraceptives should be withheld until pregnancy has been ruled out. If pregnancy is confirmed, the patient should be apprised of the potential risks to the fetus and the advisability of continuation of the pregnancy should be discussed.

Women who discontinue oral contraceptives with the intent of becoming pregnant should use an alternate form of contraception for a period of time before attempting to conceive.

Administration of progestogen-only or progestogen-estrogen combinations to induce withdrawal bleeding should not be used as a test of pregnancy.

6. *Gallbladder Disease:* Studies report an increased risk of surgically confirmed gallbladder disease in users of oral contraceptives.

7. *Carbohydrate and Lipid Metabolic Effects:* Because decreased glucose tolerance has been observed in a significant percentage of patients, prediabetic and diabetic patients should be carefully observed while receiving oral contraceptives.

An increase in triglycerides and total phospholipids has been observed.

8. *Elevated Blood Pressure:* An increase in blood pressure has been reported in patients receiving oral contraceptives. The prevalence in users increases with longer exposure. Age is also strongly correlated with development of hypertension. Women who previously have had hypertension during pregnancy may be more likely to develop elevation of blood pressure.

9. *Headache:* Onset or exacerbation of migraine or development of headache of a new pattern which is recurrent, persistent, or severe, requires discontinuation of oral contraceptives.

10. *Bleeding Irregularities:* Breakthrough bleeding, spotting, and amenorrhea are frequent reasons for patients discontinuing oral contraceptives. In breakthrough bleeding, nonfunctional causes should be borne in mind. In undiagnosed abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy.

Women with a past history of oligomenorrhea or secondary amenorrhea, or young women without regular cycles should be advised that they may have a tendency to remain anovulatory or to become amenorrheic after discontinuation of oral contraceptives.

11. *Ectopic Pregnancy:* Ectopic as well as intrauterine pregnancy may occur in contraceptive failures.

12. *Breast Feeding:* Oral contraceptives may interfere with lactation. Furthermore, a small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs.

PRECAUTIONS
1. A complete medical and family history should be taken prior to the initiation of oral contraceptives. The pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen, and pelvic organs, including Papanicolaou smear and relevant laboratory tests. As a general rule, oral contraceptives should not be prescribed for longer than one year without another examination.

2. Preexisting uterine leiomyomata may increase in size.

3. Patients with a history of psychic depression should be carefully observed and the drug discontinued if depression recurs to a serious degree.

4. Oral contraceptives may cause fluid retention and should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated.

5. Patients with a past history of jaundice during pregnancy have an increased risk of recurrence of jaundice. If jaundice develops, the medication should be discontinued.

6. Steroid hormones may be poorly metabolized and should be administered with caution in patients with impaired liver function.

7. Users may have disturbances in normal tryptophan metabolism, which may result in a relative pyridoxine deficiency.

8. Serum folate levels may be depressed.

9. The pathologist should be advised of oral contraceptive therapy when relevant specimens are submitted.

10. Certain endocrine and liver function tests and blood components may be affected.
(a) Increased sulfobromophthalein retention. (b) Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability. (c) Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone. (d) Decreased pregnanediol excretion. (e) Reduced response to metyrapone test.

Drug interactions: Reduced efficacy and increased incidence of breakthrough bleeding have been associated with concomitant use of rifampin and an association has been suggested with barbiturates, phenylbutazone, phenytoin sodium, and ampicillin.

ADVERSE REACTIONS
An increased risk of the following serious adverse reactions has been associated with oral contraceptives.

Thrombophlebitis; Pulmonary embolism; Coronary thrombosis; Cerebral thrombosis; Cerebral hemorrhage; Hypertension; Gallbladder disease; Benign hepatomas; Congenital anomalies.

There is evidence of an association between the following conditions and the use of oral contraceptives, although additional confirmatory studies are needed. Mesenteric thrombosis, Neuro-ocular lesions, eg, retinal thrombosis and optic neuritis.

The following adverse reactions have been reported in patients receiving oral contraceptives and are believed to be drug-related. Nausea and/or vomiting, usually the most common adverse reactions, occur in approximately 10 percent or less of patients during the first cycle. Other reactions, as a general rule, are seen much less frequently or only occasionally: gastrointestinal symptoms; breakthrough bleeding; spotting; change in menstrual flow; dysmenorrhea; amenorrhea during and after treatment; temporary infertility after discontinuance of treatment; edema; chloasma or melasma; breast changes; change in weight; change in cervical erosion and cervical secretion; possible diminution in lactation when given immediately post partum; cholestatic jaundice; migraine; increase in size of uterine leiomyomata; rash (allergic); mental depression; reduced tolerance to carbohydrates; vaginal candidiasis; change in corneal curvature; intolerance to contact lenses.

The following adverse reactions have been reported and the association has been neither confirmed nor refuted.

Premenstrual-like syndrome; cataracts; changes in libido; chorea; changes in appetite; cystitis-like syndrome; headache; nervousness; dizziness; hirsutism; loss of scalp hair; erythema multiforme; erythema nodosum; hemorrhagic eruption; vaginitis; porphyria.

Special Notes on Administration
Loestrin [21] 1.5/30 (1.5 mg norethindrone acetate and 30 mcg ethinyl estradiol tablets, USP) — Menstruation usually begins two or three days, but may begin as late as the fourth or fifth day, after discontinuing medication.

Loestrin [Fe] 1.5/30 — Menstruation usually begins two or three days, but may begin as late as the fourth or fifth day, after the brown ferrous fumarate tablets have been started.

Because of the relatively low estrogenic content, Loestrin 1.5/30 is not a good cyclic regulator. There are patients whose inherent hormone balance will require larger amounts of estrogen than that contained in Loestrin 1.5/30 to achieve cyclic regularity. These patients experience altered bleeding patterns, which do not conform to treatment schedules.

The physician should be alert to the fact that the irregular bleeding patterns could mask bleeding from organic cause, and appropriate diagnostic measures should be taken if the bleeding persists or continues after changing to a higher estrogen-content product.

After several months, bleeding may be reduced to a virtual absence; reduced flow may be a result of medication and not indicative of pregnancy.

HOW SUPPLIED
Loestrin [Fe] 1.5/30 is available in compacts each containing 21 green tablets and 7 brown tablets. Each green tablet contains 1.5 mg of norethindrone acetate and 30 mcg of ethinyl estradiol. Each brown tablet contains 75 mg of ferrous fumarate. Available in packages of five compacts and packages of five refills.

Loestrin [21] 1.5/30 is available in compacts each containing 21 tablets. Each green tablet contains 1.5 mg of norethindrone acetate and 30 mcg of ethinyl estradiol. Available in packages of five compacts and packages of five refills.

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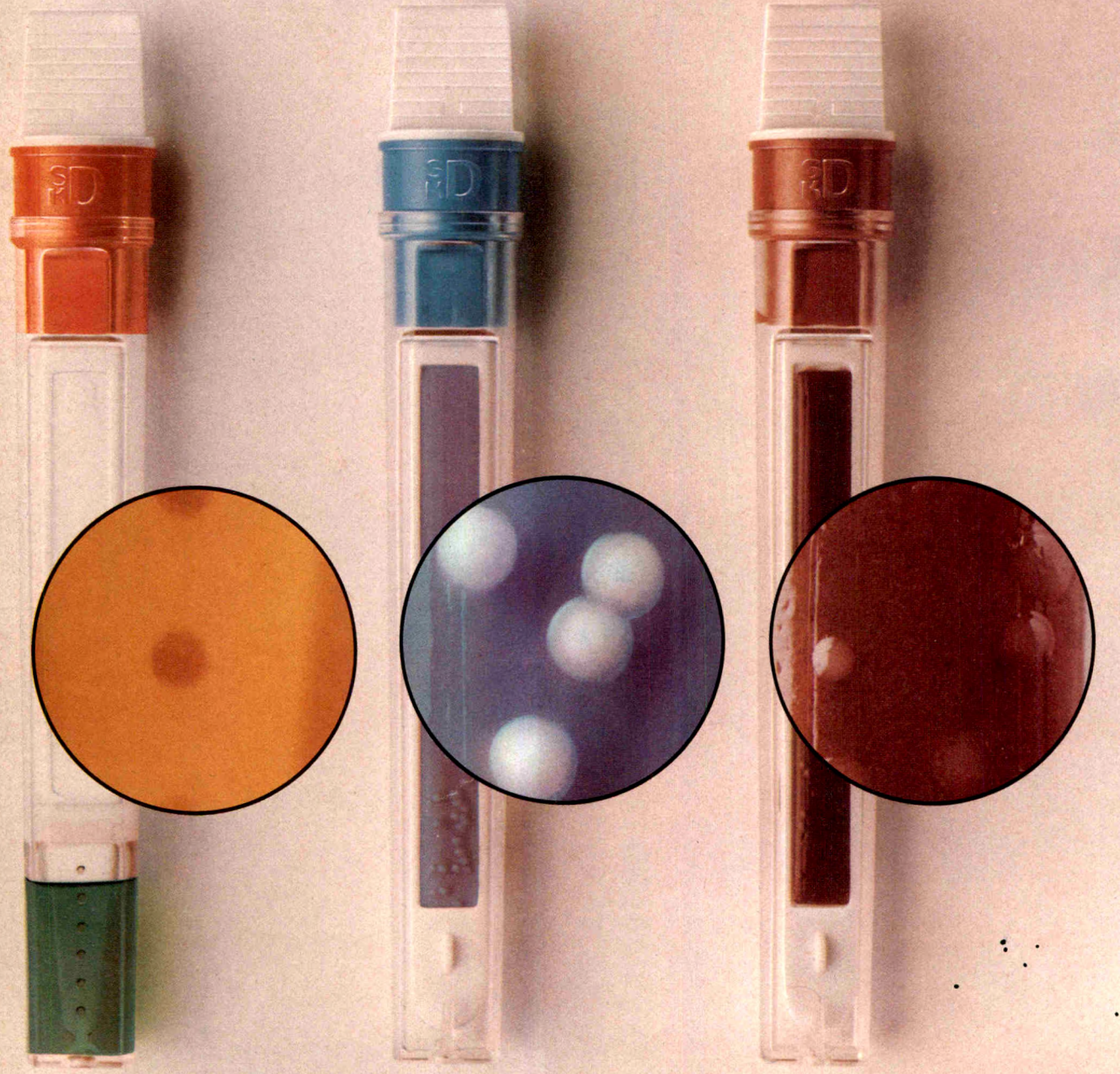
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INDICATIONS: Macrodantin is indicated for the treatment of urinary tract infections when due to susceptible strains of *Escherichia coli*, enterococci, *Staphylococcus aureus* (it is not indicated for the treatment of associated renal cortical or perinephric abscesses), and certain susceptible strains of *Klebsiella* species, *Enterobacter* species, and *Proteus* species.

NOTE: Specimens for culture and susceptibility testing should be obtained prior to and during drug administration.

CONTRAINDICATIONS: Anuria, oliguria, or significant impairment of renal function (creatinine clearance under 40 ml per minute) are contraindications to therapy with this drug. Treatment of this type of patient carries an increased risk of toxicity because of impaired excretion of the drug. For the same reason, this drug is much less effective under these circumstances.

The drug is contraindicated in pregnant patients at term as well as in infants under one month of age because of the possibility of hemolytic anemia due to immature enzyme systems (glutathione instability).

The drug is also contraindicated in those patients with known hypersensitivity to Macrodantin, Furadantin® (nitrofurantoin), and other nitrofurantoin preparations.

WARNINGS: Acute, subacute and chronic pulmonary reactions have been observed in patients treated with nitrofurantoin products. If these reactions occur, the drug should be withdrawn and appropriate measures should be taken.

An insidious onset of pulmonary reactions (diffuse interstitial pneumonitis or pulmonary fibrosis, or both) in patients on long-term therapy warrants close monitoring of these patients.

There have been isolated reports giving pulmonary reactions as a contributing cause of death. (See Hypersensitivity reactions.)

Cases of hemolytic anemia of the primaquine sensitivity type have been induced by Macrodantin. The hemolysis appears to be linked to a glucose-6-phosphate dehydrogenase deficiency in the red blood cells of the affected patients. This deficiency is found in 10 percent of Negroes and a small percentage of ethnic groups of Mediterranean and Near-Eastern origin. Any sign of hemolysis is an indication to discontinue the drug. Hemolysis ceases when the drug is withdrawn.

Pseudomonas is the organism most commonly implicated in superinfections in patients treated with Macrodantin.

PRECAUTIONS: Peripheral neuropathy may occur with Macrodantin therapy; this may become severe or irreversible. Fatalities have been reported. Predisposing conditions such as renal impairment (creatinine clearance under 40 ml per minute), anemia, diabetes, electrolyte imbalance, vitamin B deficiency, and debilitating disease may enhance such occurrence.

Usage in Pregnancy: The safety of Macrodantin during pregnancy and lactation has not been established. Use of this drug in women of childbearing potential requires that the anticipated benefit be weighed against the possible risks.

ADVERSE REACTIONS: Gastrointestinal reactions: Anorexia, nausea and emesis are the most frequent reactions; abdominal pain and diarrhea occur less frequently. These dose-related toxicity reactions can be minimized by reduction of dosage, especially in the female patient. Hepatitis occurs rarely.

Hypersensitivity reactions: Pulmonary sensitivity reactions may occur, which can be acute, subacute, or chronic.

Acute reactions are commonly manifested by fever, chills, cough, chest pain, dyspnea, pulmonary infiltration with consolidation or pleural effusion on x-ray, and eosinophilia. The acute reactions usually occur within the first week of treatment and are reversible with cessation of therapy. Resolution may be dramatic.

In subacute reactions, fever and eosinophilia are observed less often. Recovery is somewhat slower, perhaps as long as several months. If the symptoms are not recognized as being drug related and nitrofurantoin is not withdrawn, symptoms may become more severe.

Chronic pulmonary reactions are more likely to occur in patients who have been on continuous nitrofurantoin therapy for six months or longer. The insidious onset of malaise, dyspnea on exertion, cough, and altered pulmonary function are common manifestations. Roentgenographic and histologic findings of diffuse interstitial pneumonitis or fibrosis, or both, are also common manifestations. Fever is rarely prominent.

The severity of these chronic pulmonary reactions and the degree of their resolution appear to be related to the duration of therapy after the first clinical signs appear. Pulmonary function may be permanently impaired even after cessation of nitrofurantoin therapy. This risk is greater when pulmonary reactions are not recognized early.

Dermatologic reactions: Maculopapular, erythematous, or eczematous eruption, pruritus, urticaria, and angioedema.

Other sensitivity reactions: Anaphylaxis, asthmatic attack in patients with history of asthma, cholestatic jaundice, drug fever, and arthralgia.

Hematologic reactions: Hemolytic anemia, granulocytopenia, leukopenia, eosinophilia, and megaloblastic anemia. Return of the blood picture to normal has followed cessation of therapy.

Neurological reactions: Peripheral neuropathy, headache, dizziness, nystagmus, and drowsiness.

Miscellaneous reactions: Transient alopecia. As with other antimicrobial agents, superinfections by resistant organisms may occur. With Macrodantin, however, these are limited to the genitourinary tract because suppression of normal bacterial flora elsewhere in the body does not occur.

References: 1. Center for Disease Control: *National Nosocomial Infections Study Report*, Annual Summary 1976, issued February 1978. Washington, DC, U.S. Department of Health, Education, and Welfare, p 8. 2. Cooper J, et al: Diagnostic and chemoprophylactic importance of perineal microbial carriage, in Siegenthaler W, Luthy R (eds): *Current Chemotherapy*. Washington, DC, American Society for Microbiology, 1978, vol 1, pp 198-200. 3. Buckley RM, McGuckin M, MacGregor RR: Urine bacterial counts after sexual intercourse. *N Engl J Med* 298:321-324, 1978. 4. PMR Bacteriologic Report, Summer Series, 1978; a national bacteriologic monitoring service for 200 acute-care hospitals of 100 beds or more.

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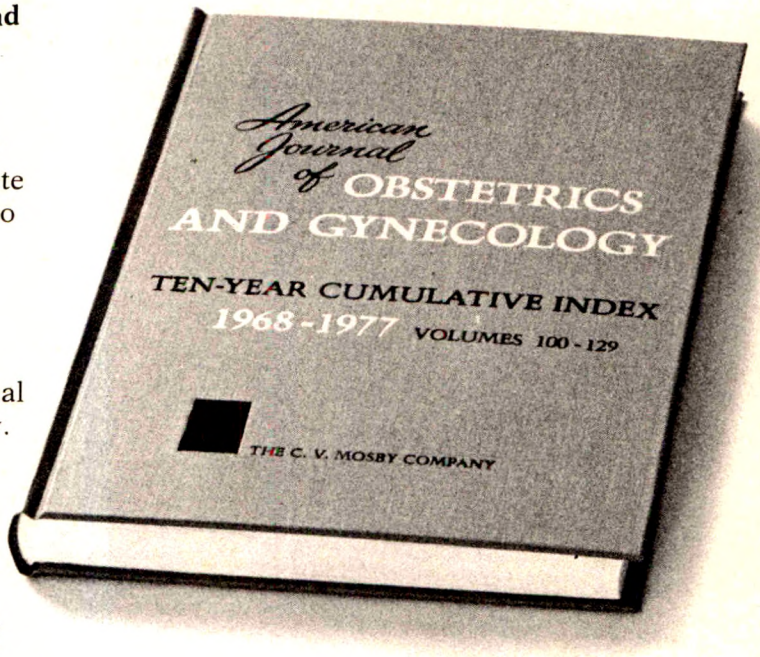


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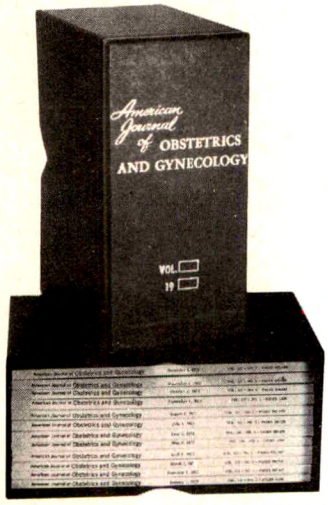
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NDICATION: CONTRACEPTION. The pregnancy rate in women using conventional combination oral contraceptives (containing 5 mcg or more of ethinyl estradiol or 50 mcg or more of mestranol) is generally reported as less than one pregnancy per 00 woman-years of use. Slightly higher rates (somewhat more than one pregnancy per 100 woman-years of use) are eported for some combination products containing 35 mcg or less of ethinyl estradiol, and rates on the order of three regnancies per 100 woman-years are reported for the progestogen-only oral contraceptives. Table 1 gives ranges of regnancy rates reported in the literature for other means of contraception. The efficacy of these means of contraception except the IUD) depends upon the degree of adherence to the method.

able 1: Pregnancies Per 100 Women-Years. IUD, less than 1-6; Diaphragm with spermicidal product (creams or jellies) 2-20; ondom, 3-36; Aerosol foams, 2-29; Jellies and creams, 4-36; Periodic abstinence (rhythm) all types, less than 1-47; 1. alendar method, 14-47; 2. Temperature method, 1-20; 3. Temperature method—intercourse only in postovulatory phase, ess than 1-7; 4. Mucus method, 1-25; No contraception, 60-80. **DOSE-RELATED RISK OF THROMBOEMBOLISM FROM ORAL ONTRACEPTIVES:** Two studies have shown a positive association between the dose of estrogens in oral contraceptives and he risk of thromboembolism. For this reason, it is prudent and in keeping with good principles of therapeutics to minimize xposure to estrogen. The oral contraceptive product prescribed for any given patient should be that product which ontains the least amount of estrogen that is compatible with an acceptable pregnancy rate and patient acceptance. It is ecommended that new acceptors of oral contraceptives be started on preparations containing .05 mg or less of estrogen.

ONTRAINDICATIONS: Oral contraceptives should not be used in women with any of the following conditions: 1. Thrombophlebitis or thromboembolic disorders. 2. A past history of deep vein thrombophlebitis or thromboembolic disorders. 3. Cerebral vascular or coronary artery disease. 4. Known or suspected carcinoma of the breast. 5. Known or suspected estrogen-dependent neoplasia. 6. Undiagnosed, abnormal genital bleeding. 7. Known or suspected pregnancy (see WARNINGS, No. 5).

WARNINGS

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

The use of oral contraceptives is associated with increased risk of several serious conditions including thromboembolism, stroke, myocardial infarction, hepatic adenoma, gallbladder disease, hypertension. Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks.

1. THROMBOEMBOLIC DISORDERS AND OTHER VASCULAR PROBLEMS. An increased risk of thromboembolic and thrombotic disease associated with the use of oral contraceptives is well established. Four principal studies in Great Britain and three in the United States have demonstrated an increased risk of fatal and nonfatal venous thromboembolism and stroke, both hemorrhagic and thrombotic. These studies estimate that users of oral contraceptives are 4 to 11 times more likely than nonusers to develop these diseases without evident cause. Overall excess mortality due to pulmonary embolism or stroke is on the order of 1.0 to 3.5 deaths annually per 100,000 users and increases with age. **CEREBROVASCULAR DISORDERS:** In a collaborative American study of cerebrovascular disorders in women with and without predisposing causes, it was estimated that the risk of hemorrhagic stroke was 2.0 times greater in users than in nonusers and the risk of thrombotic stroke was 4.0 to 9.5 times greater in users than in nonusers.

MYOCARDIAL INFARCTION: An increased risk of myocardial infarction associated with the use of oral contraceptives has been reported confirming a previously suspected association. These studies, conducted in the United Kingdom, found, as expected, that the greater the number of underlying risk factors for coronary artery disease (cigarette smoking, hypertension, hypercholesterolemia, obesity, diabetes, history of preeclamptic toxemia), the higher the risk of developing myocardial infarction, regardless of whether the patient was an oral contraceptive user or not. Oral contraceptives, however, were found to be a clear additional risk factor. The annual excess case rate (increased risk) of myocardial infarction (fatal and nonfatal) in oral contraceptive users was estimated to be approximately 7 cases per 100,000 women users in the 30-39 age group and 67 cases per 100,000 women users in the 40-44 age group. In terms of relative risk, it has been estimated that oral contraceptive users who do not smoke (smoking is considered a major predisposing condition to myocardial infarction) are about twice as likely to have a fatal myocardial infarction as nonusers who do not smoke. Oral contraceptive users who are also smokers have about a 5-fold increased risk of fatal infarction compared to users who do not smoke, but about a 10-to 12-fold increased risk compared to nonusers who do not smoke. Furthermore, the amount of smoking is also an important factor. In determining the importance of these relative risks, however, the baseline rates for various age groups must be given serious consideration. The importance of other predisposing conditions mentioned above in determining relative and absolute risks has not as yet been quantified; it is quite likely that the same synergistic action exists, but perhaps to a lesser extent. **Risk of Dose:** In an analysis of data derived from several national adverse reaction reporting systems, British investigators concluded that the risk of thromboembolism including coronary thrombosis is directly related to the dose of estrogen used in oral contraceptives. Preparations containing 100 mcg or more of estrogen were associated with a higher risk of thromboembolism than those containing 50-80 mcg of estrogen. Their analysis did suggest, however, that the quantity of estrogen may not be the sole factor involved. This finding has been confirmed in the United States. Careful epidemiological studies to determine the degree of thromboembolic risk associated with progestogen-only oral contraceptives have not been performed. Cases of thromboembolic disease have been reported in women using these products, and they should not be presumed to be free of excess risk. The risk of thromboembolic and thrombotic disorders, in both users and nonusers of oral contraceptives, increases with age. Oral contraceptives are, however, an independent risk factor for these events. **ESTIMATE OF EXCESS MORTALITY FROM CIRCULATORY DISEASES:** A large prospective study carried out in the United Kingdom estimated the mortality rate per 100,000 women per year from diseases of the circulatory system for users and nonusers of oral contraceptives according to age, smoking habits, and duration of use. The overall excess death rate annually from circulatory diseases for oral contraceptive users was estimated to be 20 per 100,000 (ages 15-34—5/100,000; ages 35-44—33/100,000; ages 45-49—140/100,000), the risk being concentrated in older women, in those with a long duration of use, and in cigarette smokers. It was not possible, however, to examine the interrelationships of age, smoking, and duration of use, nor to compare the effects of continuous versus intermittent use. Although the study showed a 10-fold increase in death due to circulatory diseases in users for five or more years, all of these deaths occurred in women 35 or older. Until larger numbers of women under 35 with continuous use for five or more years are available, it is not possible to assess the magnitude of the relative risk for this younger age group. This study reports that the increased risk of circulatory diseases may persist after the pill is discontinued. Another study published at the same time confirms a previously reported increase of mortality in pill users from cardiovascular disease. The available data from a variety of sources have been analyzed to estimate the risk of death associated with various methods of contraception. The estimates of risk of death for each method include the combined risk of the contraceptive method (e.g., thromboembolic and thrombotic disease in the case of oral contraceptives) plus the risk attributable to pregnancy or abortion in the event of method failure. This latter risk varies with the effectiveness of the contraceptive method. The findings of this analysis are shown in Figure 1 below. The study concluded that the mortality associated with all methods of birth control is low and below that associated with childbirth, with the exception of oral contraceptives in women over 40 who smoke. (The rates given for pill only/smokers for each age group are for smokers as a class. For "heavy" smokers [more than 15 cigarettes a day], the rates given would be about double; for "light" smokers [less than 15 cigarettes a day], about 50 percent.) The mortality associated with oral contraceptive use in nonsmokers over 40 is higher than with any other method of contraception in that age group. The lowest mortality is associated with the condom or diaphragm backed up by early abortion. The risk of thromboembolic and thrombotic disease associated with oral contraceptives increases with age after approximately age 30 and, for myocardial infarction, is further increased by hypertension, hypercholesterolemia, obesity, diabetes, or history of preeclamptic toxemia and especially by cigarette smoking. The risk of myocardial infarction in oral contraceptive users is substantially increased in women age 40 and over, especially those with other risk factors. Based on the data currently available, the following chart gives a gross estimate of the risk of death from circulatory disorders associated with the use of oral contraceptives.

SMOKING HABITS AND OTHER PREDISPOSING CONDITIONS—RISK ASSOCIATED WITH USE OF ORAL CONTRACEPTIVES

Age	Below 30	30-39	40+	
Heavy smokers	C	B	A	A—Use associated with very high risk.
Light smokers	D	C	B	B—Use associated with high risk.
Nonsmokers (no predisposing conditions)	D	C,D	C	C—Use associated with moderate risk.
Nonsmokers (other predisposing conditions)	C	C,B	B,A	D—Use associated with low risk.

The physician and the patient should be alert to the earliest manifestations of thromboembolic and thrombotic disorders (e.g., thrombophlebitis, pulmonary embolism, cerebrovascular insufficiency, coronary occlusion, retinal thrombosis, and mesenteric thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately. A four- to six-fold increased risk of postsurgery thromboembolic complications has been reported in oral contraceptive users. If feasible, oral contraceptives should be discontinued at least four weeks before surgery of a type associated with an increased risk of thromboembolism or prolonged immobilization. 2. OCULAR LESIONS: There have been reports of neuro-ocular lesions such as optic neuritis or retinal thrombosis associated with the use of oral contraceptives. Discontinue oral contraceptive medication if there is unexplained, sudden or gradual, partial or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal vascular lesions and institute appropriate diagnostic and therapeutic measures. 3. CARCINOMA. Long-term continuous administration of either natural or synthetic estrogen in certain animal species increases the frequency of carcinoma of the breast, cervix, vagina, and liver. Certain synthetic progestogens, none currently contained in oral contraceptives, have been noted to increase the incidence of mammary nodules, benign and malignant, in dogs. In humans, three case control studies have reported an increased risk of endometrial carcinoma associated with the prolonged use of exogenous estrogen in postmenopausal women. One publication reported on the first 21 cases submitted by physicians to a registry of cases of adenocarcinoma of the endometrium in women under 40 on oral contraceptives. Of the cases found in women without predisposing risk factors for adenocarcinoma of the endometrium (e.g., irregular bleeding at the time oral contraceptives were first given, polycystic ovaries), nearly all occurred in women who had used a sequential oral contraceptive. These products are no longer marketed. No evidence has been reported suggesting an increased risk of endometrial cancer in users of conventional combination or progestogen-only oral contraceptives. Several studies have found no increases in breast cancer in women taking oral contraceptives or estrogens. One study, however, while also noting no overall increased risk of breast cancer in women treated with oral contraceptives, found an excess risk in the subgroups of oral contraceptive users with documented benign breast disease. A reduced occurrence of benign breast tumors in users of oral contraceptives has been well-documented. In summary, there is at present no confirmed evidence from human studies of an increased risk of cancer associated with oral contraceptives. Close clinical surveillance of all women taking oral contraceptives is, nevertheless, essential. In all cases of undiagnosed persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be taken to rule out malignancy. Women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease or abnormal mammograms should be monitored with particular care if they elect to use oral contraceptives instead of other methods of contraception. *Trademark

women, by regimen of control and age of woman.

	15-19	20-24	25-29	30-34	35-39	40-44
No method	5.5	5.2	7.1	14.0	19.3	21.9
Abortion only	2.3	2.5	2.5	5.2	9.8	6.6
Pill only-nonsmokers	1.3	1.4	1.4	2.2	4.5	3.1
Pill only-smokers	1.5	1.6	1.6	10.8	13.4	58.9
IUDs only	1.1	1.2	1.2	1.4	1.6	1.4
Traditional contraception only	1.1	1.4	1.9	3.7	4.7	4.0
Traditional contraception and abortion	0.3	0.4	0.4	0.8	1.4	0.8

4. HEPATIC TUMORS. Benign hepatic adenomas have been found to be associated with the use of oral contraceptives. One study showed that oral contraceptive formulations with high hormonal potency were associated with a higher risk than lower potency formulations. Although benign, hepatic adenomas may rupture and may cause death through intra-abdominal hemorrhage. This has been reported in short-term as well as long-term users of oral contraceptives. Two studies relate risk with duration of use of the contraceptive, the risk being much greater after four or more years of oral contraceptive use. While hepatic adenoma is a rare lesion, it should be considered in women presenting abdominal pain and tenderness, abdominal mass or shock. A few cases of hepatocellular carcinoma have been reported in women taking oral contraceptives. The relationship of these drugs to this type of malignancy is not known at this time. 5. USE IN OR IMMEDIATELY PRECEDING PREGNANCY, BIRTH DEFECTS IN OFFSPRING, AND MALIGNANCY IN FEMALE OFFSPRING. The use of female sex hormones—both estrogenic and progestational agents—during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a nonsteroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare. This risk has been estimated to be on the order of 1 to 4 in 1000 exposures. Although there is no evidence at the present time that oral contraceptives further enhance the risk of developing this type of malignancy, such patients should be monitored with particular care if they elect to use oral contraceptives instead of other methods of contraception. Furthermore, a high percentage of such exposed women (from 30 to 90%) have been found to have epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether this condition is a precursor of vaginal malignancy. Male children so exposed may develop abnormalities of the urogenital tract. Although similar data are not available with the use of other estrogens, it cannot be presumed that they would not induce similar changes. An increased risk of congenital anomalies, including heart defects and limb defects, has been reported with the use of sex hormones, including oral contraceptives, in pregnancy. One case control study has estimated a 4.7-fold increase in risk of limb-reduction defects in infants exposed in utero to sex hormones (oral contraceptives, hormonal withdrawal tests for pregnancy or attempted treatment for threatened abortion). Some of these exposures were very short and involved only a few days of treatment. The data suggest that the risk of limb-reduction defects in exposed fetuses is somewhat less than one in 1,000 live births. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well-controlled studies that progestogens are effective for these uses. There is some evidence that triploidy and possibly other types of polyploidy are increased among abortuses from women who become pregnant soon after ceasing oral contraceptives. Embryos with these anomalies are virtually always aborted spontaneously. Whether there is an overall increase in spontaneous abortion of pregnancies conceived soon after stopping oral contraceptives is unknown. It is recommended that for any patient who has missed two consecutive periods, pregnancy should be ruled out before continuing the contraceptive regimen. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at the time of the first missed period (or after 45 days from the last menstrual period if the progestogen-only oral contraceptives are used), and further use of oral contraceptives should be withheld until pregnancy has been ruled out. If pregnancy is confirmed, the patient should be apprised of the potential risks to the fetus and the advisability of continuation of the pregnancy should be discussed in the light of these risks. It is also recommended that women who discontinue oral contraceptives with the intent of becoming pregnant use an alternate form of contraception for a period of time before attempting to conceive. Many clinicians recommend three months although no precise information is available on which to base this recommendation. The administration of progestogen-only or progestogen-estrogen combinations to induce withdrawal bleeding should not be used as a test of pregnancy. 6. GALLBLADDER DISEASE. Studies report an increased risk of surgically confirmed gallbladder disease in users of oral contraceptives and estrogens. In one study, an increased risk appeared after two years of use and doubled after four or five years of use. In one of the other studies, an increased risk was apparent between six and twelve months of use. 7. CARBOHYDRATE AND LIPID METABOLIC EFFECTS. A decrease in glucose tolerance has been observed in a significant percentage of patients on oral contraceptives. For this reason, prediabetic and diabetic patients should be carefully observed while receiving oral contraceptives. An increase in triglycerides and total phospholipids has been observed in patients receiving oral contraceptives. The clinical significance of this finding remains to be defined. 8. ELEVATED BLOOD PRESSURE. An increase in blood pressure has been reported in patients receiving oral contraceptives. In some women hypertension may occur within a few months of beginning oral contraceptive use. In the first year of use, the prevalence of women with hypertension is low in users and may be no higher than that of a comparable group of nonusers. The prevalence in users increases, however, with longer exposure, and in the fifth year of use is two and a half to three times the reported prevalence in the first year. Age is also strongly correlated with the development of hypertension in oral contraceptive users. Women who previously have had hypertension during pregnancy may be more likely to develop elevation of blood pressure when given oral contraceptives. Hypertension that develops as a result of taking oral contraceptives usually returns to normal after discontinuing the drug. 9. HEADACHE. The onset or exacerbation of migraine or development of headache of a new pattern which is recurrent, persistent, or severe, requires discontinuation of oral contraceptives and evaluation of the cause. 10. BLEEDING IRREGULARITIES. Breakthrough bleeding, spotting, and amenorrhea are frequent reasons for patients discontinuing oral contraceptives. In breakthrough bleeding, as in all cases of irregular bleeding from the vagina, nonfunctional causes should be borne in mind. In undiagnosed persistent or recurrent abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy. If pathology has been excluded, time or a change to another formulation may solve the problem. Changing to an oral contraceptive with a higher estrogen content, while potentially useful in minimizing menstrual irregularity, should be done only if necessary since this may increase the risk of thromboembolic disease. Women with a past history of oligomenorrhea or secondary amenorrhea or young women without regular cycles may have a tendency to remain anovulatory or to become amenorrheic after discontinuation of oral contraceptives. Women with these preexisting problems should be advised of this possibility and encouraged to use other contraceptive methods. Postuse anovulation, possibly prolonged, may also occur in women without previous irregularities. 11. ECTOPIC PREGNANCY. Ectopic as well as intrauterine pregnancy may occur in contraceptive failures. 12. BREAST FEEDING. Oral contraceptives given in the postpartum period may interfere with lactation. There may be a decrease in the quantity and quality of the breast milk. Furthermore, a small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs. The effects, if any, on the breast-fed child have not been determined. If feasible, the use of oral contraceptives should be deferred until the infant has been weaned. **PRECAUTIONS: General:** 1. A complete medical and family history should be taken prior to the initiation of oral contraceptives. The pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen and pelvic organs, including Papanicolaou smear and relevant laboratory tests. As a general rule, oral contraceptives should not be prescribed for longer than one year without another physical examination being performed. 2. Under the influence of estrogen-progestogen preparations, preexisting uterine leiomyomata may increase in size. 3. Patients with a history of psychic depression should be carefully observed and the drug discontinued if depression recurs to a serious degree. Patients becoming significantly depressed while taking oral contraceptives should stop the medication and use an alternate method of contraception in an attempt to determine whether the symptom is drug-related. 4. Oral contraceptives may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention, such as convulsive disorders, migraine syndrome, asthma, or cardiac or renal insufficiency. 5. Patients with a past history of jaundice during pregnancy have an increased risk of recurrence of jaundice while receiving oral contraceptive therapy. If jaundice develops in any patient receiving such drugs, the medication should be discontinued. 6. Steroid hormones may be poorly metabolized in patients with impaired liver function and should be administered with caution in such patients. 7. Oral contraceptive users may have disturbances in normal tryptophan metabolism which may result in a relative pyridoxine deficiency. The clinical significance of this is yet to be determined. 8. Serum folate levels may be depressed by oral contraceptive therapy. Since the pregnant woman is predisposed to the development of folate deficiency and the incidence of folate deficiency increases with increasing gestation, it is possible that if a woman becomes pregnant shortly after stopping oral contraceptives, she may have a greater chance of developing folate deficiency and complications attributed to this deficiency. 9. The pathologist should be advised of oral contraceptive therapy when relevant specimens are submitted. 10. Certain endocrine and liver function tests and blood components may be affected by estrogen-containing oral contraceptives: a. Increased sulfobromophthalein retention. b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability. c. Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG, free T4 concentration is unaltered. d. Decreased pregnanediol excretion. e. Reduced response to metyrapone test. **INFORMATION FOR THE PATIENT: (See Patient Package Insert). DRUG INTERACTIONS:** Reduced efficacy and increased incidence of breakthrough bleeding have been associated with concomitant use of rifampin. A similar association has been suggested with barbiturates, phenylbutazone, phenytoin sodium, and ampicillin. **CARCINOGENESIS, PREGNANCY, NURSING MOTHERS: See CONTRAINDICATIONS and WARNINGS. ADVERSE REACTIONS:** An increased risk of the following serious adverse reactions has been associated with the use of oral contraceptives (see WARNINGS): Thrombophlebitis. Pulmonary embolism. Coronary thrombosis. Cerebral thrombosis. Cerebral hemorrhage. Hypertension. Gallbladder disease. Liver tumors. Congenital anomalies. There is evidence of an association between the following conditions and the use of oral contraceptives, although additional confirmatory studies are needed: Mesenteric thrombosis. Neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis. The following adverse reactions have been reported in patients receiving oral contraceptives and are believed to be drug-related: Nausea, usually the most common adverse reaction. Vomiting, occurs in approximately 10% or less of patients during the first cycle. Other reactions, as a general rule, are seen much less frequently or only occasionally. Gastrointestinal symptoms (such as abdominal cramps and bloating). Breakthrough bleeding. Spotting. Change in menstrual flow. Dysmenorrhea. Amenorrhea during and after treatment. Temporary infertility after discontinuance of treatment. Edema. Chloasma or melasma which may persist. Breast changes: tenderness, enlargement, and secretion. Change in weight (increase or decrease). Change in cervical erosion and cervical secretion. Possible diminution in lactation when given immediately postpartum. Cholestatic jaundice. Migraine. Increase in size of uterine leiomyomata. Rash (allergic). Mental depression. Reduced tolerance to carbohydrates. Vaginal candidiasis. Change in corneal curvature (steepening). Intolerance to contact lenses. The following adverse reactions have been reported in users of oral contraceptives, and the association has been neither confirmed nor refuted: Premenstrual-like syndrome. Cataracts. Changes in libido. Chorea. Changes in appetite. Cystitis-like syndrome. Headache. Nervousness. Dizziness. Hirsutism. Loss of scalp hair. Erythema multiforme. Erythema nodosum. Hemorrhagic eruption. Vaginitis. Porphyria. Impaired renal function. (ORTHO-NOVUM 1/50 21 and ORTHO-NOVUM 1/50 28 contain tartrazine. Allergic reactions have been reported with the ingestion of this dye in some patients.) **ACUTE OVERDOSE:** Serious ill effects have not been reported following acute ingestion of large doses of oral contraceptives by young children. Overdosage may cause nausea, and withdrawal bleeding may occur in females.

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THE DIABETIC PREGNANCY

A Perinatal Perspective

Edited by IRWIN R. MERKATZ, M.D. and PETER A. J. ADAM, M.D.

This book presents recent advances in the basic concepts of pregnancy complicated by maternal diabetes and relates this scientific knowledge to an evolving rationale for clinical practice. In the first part of the book, metabolic adjustments to normal and diabetic pregnancies are discussed, and the clinical management of such disorders as diabetic nephropathy and proliferative retinopathy in relation to pregnancy is established. The authors assess the roles of psychology, nutrition and family planning in the management of the pregnant diabetic woman. The second part of the book considers the effects of maternal diabetes on the placenta and fetus, and the third part is concerned with the biochemical, physiologic and pathologic implications for the infant of the diabetic mother.

1979, 384 pp., $34.50 ISBN: 0-8089-1175-9

BREAST DISEASE

Edited by DOUGLAS J. MARCHANT, M.D. and ISTVAN NYIRJESY, M.D.

Proceedings of an International Symposium held in New Orleans, May 1978.

This book reflects the involvement of many specialties. The family physician is interested in identifying high risk patients and promoting breast self examination and early detection. The obstetrician/gynecologist, the primary physician to women, is most frequently consulted for the diagnosis and treatment of benign conditions appearing principally during the reproductive years. Alterations in the hormone milieu which produce amenorrhea and/or galactorrhea provide a unique interface between obstetrics, gynecology and endocrinology. The chapters provide an overview of breast disease including pathophysiology, detection, diagnosis and treatment. A persuasive case is made for the selective and non-operative treatment of breast carcinoma. Diagnostic studies include the thermographic measurement of metabolic activity of tumors and the interpretation of increasingly sophisticated imaging techniques—sonography and mammography.

1979, 336 pp., $19.50 ISBN: 0-8009-1177-5

REVERSIBILITY OF FEMALE STERILIZATION

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The book comprises the proceedings of a symposium devoted to sterilization and its reversal. Emphasis is on technical aspects with discussions of basic Fallopian tube anatomy, physiology, and pathology, and the application of microsurgical techniques. The chapters provide practical guidelines for the gynecologist and also a stimulus for further investigation of this important aspect of human reproduction.

Edition for the Americas published by Grune & Stratton

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NEW ADVANCES IN THE TREATMENT OF CANDIDAL VAGINITIS

Edited by D. GOUGH

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The chapters include: Cure and Relapse of Candidal Vaginitis Following Treatment with Miconazole, Clotrimazole and Nystatin; The Efficacy of Seven Day Administration of Miconazole in Candidal Vaginitis. The Influence of Dosage and Times of Administration of Miconazole on Cure of Candidal Vaginitis; New Gynecologic Formulations of Miconazole; A Study of the Cure and Relapse of Candidal Vaginitis With A Novel Formulation of Miconazole.

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CLINICAL OPINION

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Modern management of the breech delivery

LEON I. MANN, M.D.
JANICE M. GALLANT, P.A.-C.
Burlington, Vermont

Retrospective review of 457 breech deliveries failed to reveal a significant improvement in neonatal mortality and morbidity rates for those delivered by cesarean section vs. vaginal delivery. A slight but insignificant improvement in salvage was found for the 1,000 to 1,500 gram weight category when delivery was by cesarean section. Most of the deaths in the less than 1,500 gram breech presentation were associated with hyaline membrane disease or congenital defects incompatible with life and sepsis rather than directly related to the manner of breech delivery. (AM. J. OBSTET. GYNECOL. 134:611, 1979.)

PROPER OBSTETRIC management of the breech presentation has been discussed and debated for many years.[1-3] There is still no unanimity of opinion regarding the safest method of delivery. In an attempt to decrease the incidence of intrapartum breech, external cephalic version prior to labor has been recommended, particularly since the introduction of uterine relaxing agents. This procedure, however, has not gained widespread acceptance so that the same number of intrapartum breech presentations continues to occur per year. Increased concern with perinatal death, quality of life in terms of short- and long-term morbidity, and the threat of malpractice litigation resulting from poor obstetric outcome has led some to suggest that all breech presentations should be delivered by cesarean section. Management based upon objective criteria of pelvic capacity, fetal size, and progress of labor and subjective evaluation by training and experience has been said to have no place in the modern management of the breech presentation. Many obstetricians and institutions have instituted management protocols that involve cesarean section for all breech presentations. As a result, the rate of cesarean section for breech

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Table I. Breech deliveries*

	Per cent
Age:	
11-20	108- 24
21-30	288- 63
31-40	61- 13
Parity:	
0	197- 43
1-3	216- 47
>3	44- 10
Type of breech:	
Frank	200- 44
Complete	144- 32
Footling	108- 24
Compound	5-<1

*Total deliveries, 11338. Breech presentation, 457. Per cent of deliveries, 4.

presentations has risen dramatically during the past decade. This has occurred simultaneously with an increased rate of cesarean section for other perinatal complications. The obstetric community is now being challenged to defend this increased cesarean section rate. Review of the literature reveals few articles that provide a scientific—much less statistical—basis to support cesarean section for all breech presentations. The present study was undertaken to evaluate our own experience with vaginal vs. abdominal delivery for the breech presentations.

Study population and methods

The study involved 457 breech deliveries that occurred during a total of 11,338 deliveries—an incidence of 4%. The charts were reviewed for age, parity, type of breech, Apgar scores at 1 and 5 minutes, and fetal and neonatal deaths. Twins were included in the study only when Twin A presented as a breech. There was no established protocol for management of the breech during the time period of the study. Spontaneous delivery to the umbilicus followed by rapid general anesthesia and assisted breech delivery was the method used in most cases of vaginal delivery. Forceps to the aftercoming head were not applied routinely. A low-flap transverse uterine incision was used for the cesarean section. An anesthesiologist and neonatologist were in attendance at delivery. Long-term evaluation of the infant was unavailable for analysis.

Statistical analysis was accomplished by the comparison of two proportions. A P value of less than 0.05 was accepted as significant.

Results

General characteristics. The age, parity, and type of breech are presented in Table I: 63% of the patients were between the ages of 21 and 30 years; 43% of the patients were primiparas and 57% multiparas. The most common type of breech was the frank (44%); the complete and footling variety represented 32 and 24% of the cases.

Incidence of cesarean section by weight. The incidence of cesarean section by weight is shown in Table II. Of the 436 liveborns, 149 (34%) were delivered by cesarean section. Of the five patients delivered by cesarean section in the 500 to 999 gram category, four weighed more than 900 grams. The highest percentage of cesarean section occurred in the 1,000 to 1,499 gram category (40%).

Method of delivery and Apgar score. The Apgar scores at 1 and 5 minutes, grouped by method of delivery, are shown in Tables III and IV: 36% of the neonates had a 1 minute Apgar score between 1 and 6; 9.6% a 5 minute Apgar score between 1 and 6. There were no significant differences in depressed Apgar scores when analyzed by method of delivery and newborn weight.

Perinatal and neonatal deaths by method of delivery. Perinatal deaths for infants weighing more than 500 grams and 1,000 grams are shown in Table V. The perinatal mortality rate for the group over 1,000 grams was 56/1,000 which is approximately 6 times that for the year 1977 at the Medical Center Hospital of Vermont (9.8/1,000).

Tables VI and VII show the absolute neonatal mortality incidence and the neonatal mortality rate expressed per 1,000 live births. Neonatal death was chosen specifically as a means of evaluating method of delivery rather than perinatal death, which includes fetal deaths. There were 21 fetal deaths in the study. There was one neonatal death in 334 fetuses weighing more than 2,000 grams. This death occurred following an elective cesarean section and was the result of congenital pulmonary hypoplasia. There was no effect of parity or timing of the cesarean section, whether elective or following labor, on neonatal outcome.

The actual neonatal mortality rate per 1,000 live births in the 1,500 to 1,999 grams category was slightly higher for the cesarean section category. Of the four deaths in this weight group, two were associated with congenital defects incompatible with life, one with sepsis, and one with hyaline membrane disease.

Ten of the 25 neonates in the 1,000 to 1,499 gram group died during the neonatal period. There was a slightly improved neonatal mortality rate in the group delivered by cesarean section. This was not statistically significant. Four of these 10 deaths were associated with congenital defects incompatible with life and three were associated with sepsis and hyaline membrane disease.

Table II. Incidence of cesarean section in breech presentations

	Weight (Gm.)				
	500-999	*1,000-1,499*	*1,500-1,999*	*>2,000*	*Total*
Cesarean section deliveries:					
Number	5/34	10/25	9/43	125/334	149/436
Per cent	15	40	21	37	34

Table III. Method of delivery and 1 minute Apgar score in breech presentations

Method of delivery	*1 min. Apgar score*		
	1-6	*7-10*	*Total*
Vaginal:			
Number	109	170	279
Per cent	39	61	
Cesarean section:			
Number	46	111	157
Per cent	29	71	
Total:			
Number	155	281	436
Per cent	36	64	

Table IV. Method of delivery and 5 minute Apgar score in breech presentations

Method of delivery	*5 min. Apgar score*		
	1-6	*7-10*	*Total*
Vaginal:			
Number	27	252	279
Per cent	9.7	90.3	
Cesarean section:			
Number	15	142	157
Per cent	9.6	90.4	
Total:			
Number	42	394	436
Per cent	9.6	90.4	

Of the 34 neonates in the 500 to 999 gram group, 31 died during the neonatal period. Of these, the majority were associated with hyaline membrane disease. There was no significant improvement in the neonatal mortality rate when delivery was by cesarean section.

Table V. Perinatal deaths in breech deliveries

Weight	*No.*	*Rate*
>500 grams:		
Fetal deaths	21	46/1,000
Neonatal deaths	46	106/1,000
Perinatal deaths	67	147/1,000
>1,000 grams:		
Fetal deaths	8	19/1,000
Neonatal deaths	15	37/1,000
Perinatal deaths	23	56/1,000

Comment

The observations reported in this study do not support the recommendation that all breech presentations should be delivered by cesarean section. The results clearly indicate that the fetus weighing 2,000 grams or greater, at approximately 34 weeks or longer, need not be delivered routinely by cesarean section to improve the perinatal mortality and morbidity rates. Only one fetal death occurred in this group and that was unrelated to the breech presentation. Improved perinatal salvage following cesarean section could not be confirmed whether the patient was primiparous or multiparous or whether the section was performed electively or following a course of labor. This does not mean, however, that all breech presentations weighing 2,000 grams or more can be safely delivered vaginally. Rather, it would seem to indicate that in this weight group of breech presentations, the mother can be allowed to labor after proper evaluation of fetal-pelvic relationships and documented evidence of continuous progress by objective criteria of effacement, dilatation, and descent without arrest. Intrapartum monitoring should be conducted routinely. If hyperextension of the fetal head, fetal-pelvic disproportion, or arrest of labor were observed, cesarean section should be performed. While forceps application to the aftercoming head was not performed routinely during vaginal delivery in this study, the literature would seem to substantiate the routine application of forceps.[4] The aftercoming head of the breech that is delivered through a uterine incision similarly requires adequate room so that a wide transverse incision or a low vertical incision would seem appropriate. With this method of management of the breech presentation, a higher section rate than for vertex presentation should be anticipated. What the ideal cesarean section rate will be is difficult to state, but a range of 20 to 30% seems appropriate.

Results obtained in the present study for the breech fetus weighing more than 1,500 grams but less than 2,000 grams show an increased mortality rate when compared to those over 2,000 grams. Cesarean section did not, however, improve the mortality rate in this

Table VI. Method of delivery and neonatal deaths in breech presentations

Method of delivery	*Weight (Gm.)*				
	500-999	*1,000-1,499*	*1,500-1,999*	*>2,000*	*Total*
Vaginal	27/29	7/15	3/34	0/209	37/287
Cesarean section	4/5	3/10	1/9	1/125	9/149
Total	31/34	10/25	4/43	1/334	46/436
				>1,000	15/402

Table VII. Method of delivery and neonatal deaths per 1,000 live births in breech presentations

Method of delivery	*Weight (Gm.)*				
	500-999	*1,000-1,499*	*1,500-1,999*	*>2,000*	*Total*
Vaginal	931	467	88	0	129
Cesarean section	800	300	111	8	60
Total	912	400	93	3	106
				>1,000	37

group. None of the neonatal deaths was related to the breech delivery per se. Other reports have revealed similar findings.

For the total group above 1,500 grams, therefore, no improvement in the perinatal mortality rate could be demonstrated by cesarean section. These results are in disagreement with the large retrospective study of breeches reported from Finland.[5] The differences are not readily explicable.

The breech fetuses weighing between 1,000 and 1,500 grams were too few to allow conclusions to be made regarding the proper method of management for this weight group. There was no statistically significant difference between groups, although a slightly better rate was obtained when delivery was by cesarean section. Similar observations have been reported by others for this weight category.[6] It may be that it is this group that is best managed by cesarean section. This argument must be countered, however, by the observation that most of these fetuses died of congenital defects incompatible with life, infection, or hyaline membrane disease rather than as a direct result of the breech delivery. The neonatal mortality rate is significantly higher whether delivery is vaginal or by cesarean section so that it is impossible to conclude from available data the safest route of delivery for this weight group of breech fetuses. Each case must clearly be individualized and cesarean section selected after careful evaluation. However, a positive statement for routine cesarean section for this group does not seem warranted at this point.

This study was not prospective nor controlled and must be interpreted accordingly. In addition, it does not address long-term morbidity as it relates to the method of breech delivery. Within the constraints of the data provided by the study, however, it would seem proper to summarize that all breech presentations do not require cesarean section for safe delivery.

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Vaginal breech delivery or cesarean section

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In 579 singleton breech deliveries the total perinatal mortality rate was 10.4% and the corrected perinatal mortality rate was 0.67%. There were 452 babies delivered vaginally (78.1%) and 127 delivered by cesarean section (21.9%). The perinatal mortality rate was very high in the premature breech delivery and in the low-birth-weight infant. Cesarean section should be used to avoid a traumatic vaginal delivery and it should be used more liberally in the mature breech, but it is unlikely that cesarean section rates in excess of 50% will significantly reduce the perinatal mortality rate. More information is required as to whether extending the indications for cesarean section in the low-birth-weight infant will further reduce the perinatal mortality rate. (AM. J. OBSTET. GYNECOL. 134:615, 1979.)

IN 1977 ONE OF US (B.V.L.) visited obstetric centers in North America. During discussions with residents and staff it was apparent that there were many conflicting views as to the management of breech confinement.

The question was raised again at a debate by the Section of Obstetrics in the Royal Society of Medicine, London. Drs. H. Roberts and Fraser of London proposed that all breech presentations should be delivered by cesarean section. The motion was opposed by Drs. Edward Cope, from Oxford, and A. Barry, from Dublin. Following debate the motion was overwhelmingly defeated by the members present.

Because of the widely divergent views in the management of a common obstetric problem it seemed relevant to review, retrospectively, a relatively large number of breech confinements in a single obstetric unit.

Accordingly, 579 breech deliveries are reviewed.

Results

Between 1970 and 1976 inclusive there were 13,607 deliveries, of which 579 were singleton breech presentations—an incidence of 4.3%. The uncorrected perinatal mortality rate for all breech deliveries, both abdominal and vaginal, was 10.4% (Table I).

Of the 579 breech deliveries, 452 (78.1%) were delivered vaginally and 127 (21.9%) were delivered by cesarean section. Vaginal delivery was usually accomplished by a resident using bilateral pudendal block or epidural anesthesia and assisted or spontaneous delivery of the trunk. The arms were delivered from a flexed position across the chest or Lövset's maneuver was used to deliver the extended arms. In the United Kingdom the Burns-Marshall method is usually preferred for the aftercoming head. Forceps were frequently applied and in all cases a generous episiotomy was performed.

Table I. Singleton breech deliveries—Watford General Hospital, 1970 to 1976

Total deliveries	*Singleton breech*	*Uncorrected perinatal deaths*
13,607	579 (4.3%)	62 (10.4%)

Cesarean section was performed if the pelvic measurements were small, when there was a bad obstetric history or an elderly primigravida, especially if there had been a problem of infertility. Other relative indications included antepartum bleeding, large fetus, flexed legs, and pre-eclampsia. In labor absolute indications were fetal distress, prolapse of the umbilical cord, and failure to progress. Of the 127 cesarean sections performed 72 (56.7%) were elective and 55 (43.3%) were emergency (Table II). Seventy-five per cent of primigravidas and 81.1% of multigravidas were delivered vaginally (Table III).

Of primigravidas under 20 years of age, 85.7% were delivered vaginally compared with 33.3% of primigravidas over 35 years of age (Table IV).

Method of delivery in relation to gestational age and fetal weight. Of all breech deliveries, 86.7% had

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Table II. Singleton breech deliveries—method of delivery

Total breech presentations	*Vaginal deliveries*	*Cesarean section*	*Elective cesarean section*	*Emergency cesarean section*
579	452 (78.1%)	127 (21.9%)	72 (56.7%)	55 (43.3%)

Table III. Method of delivery according to parity

		Vaginal delivery		*Cesarean section*		*Elective cesarean section*	
	No.	*No.*	*%*	*No.*	*%*	*No.*	*%*
Primipara	293	220	75	73	25	36	49.3
Multipara	286	232	81.8	54	18.9	36	66.7
Total	579	352	78.1	127	21.9	72	

Table IV. Method of delivery in young and old primigravidas with breech presentation

	Age (yr.)	*Vaginal delivery (%)*	*Cesarean section (%)*
Primiparas	<20	85.7	14.3
Primiparas	>35	33.3	66.7

Table V. Perinatal deaths in breech pregnancies

	Uncorrected		*Corrected*	
	No.	*%*	*No.*	*%*
Stillbirths	38	61.3 *	3	75 *
Neonatal deaths	24	38.7 *	1	25 *
Perinatal deaths	62	10.4	4	0.67

*Per cent perinatal deaths.

Table VI. Perinatal deaths and birth weight

Weight (Gm.)	*Stillbirths*		*Neonatal deaths*		*Perinatal deaths (%)*
	No.	*%*	*No.*	*%*	
1,000	15	39.5	10	41.7	100
1,500	7	18.4	7	29.2	60.9
2,000	10	26.3	5	20.8	15.5
2,500	5	13.2	2	8.3	1.6
Unknown	1	2.6			
	38	100	24	100	

completed 35 weeks, leaving 13% delivered prior to week 36 of pregnancy. The hospital rate for deliveries before week 36 varied between 4 and 7%, so that there was a preponderance of breech deliveries in the premature group. Almost a quarter of all breeches delivered (24.2%) weighed less than 2,500 grams, so that there was a higher proportion of light-for-dates babies in those who had completed 35 weeks of pregnancy.

Perinatal deaths in breech pregnancies. The uncorrected perinatal death rate in all breech deliveries was 10.4% (62 out of 579), of which 38 babies (61.3%) were stillborn and 24 babies (38.7%) died within the first 7 days. The corrected perinatal death rate (corrected for low birth weight, congenital abnormality, antepartum stillbirth, Rh incompatability, etc.) was 0.67%, i.e., four deaths directly attributable to the breech presentation and errors of management (Table V). There was also a group of babies who died from multiple causes in which the breech delivery could have been a factor. Included in this group were severe pre-eclampsia, respiratory distress, and cord complications.

Perinatal death and birth weight. In babies born weighing less than 1,000 grams the perinatal mortality rate was 100%. With increasing increments in birth weight the perinatal mortality rate progressively fell until a perinatal mortality rate of 1.6% was achieved for breech babies born weighing over 2,500 grams (Table VI). The numbers involved were relatively few but there seemed to be a preponderance of stillbirths over neonatal deaths in babies whose birth weight was greater than 1,500 grams, whereas most of the neonatal deaths were in the very small weight category.

Perinatal death and gestational age. Perinatal deaths fell from 93.75% at a gestational age of less than 28 weeks to 1.9% between the end of week 37 and term. Again numbers are small but there seems to be a high perinatal mortality rate in the 34 to 36 week age.

Perinatal death and method of delivery. In the 452 patients delivered vaginally the perinatal mortality rate was 11.9% or, if macerated stillborn infants are excluded, 8.2%. In the 127 patients delivered by cesarean section the perinatal mortality rate was 6.3%. Thus the total uncorrected perinatal mortality rate for all modes of delivery was 10.4%.

Fetal loss due to breech. There were four babies who died in which the breech presentation was the cause. Retrospective review of the details show that cesarean section was delayed. Elective cesarean section would most likely have resulted in healthy babies.

Comment

We have dealt solely with perinatal deaths (stillbirths and first week deaths) and have excluded other information. We have not discussed Apgar scores at birth, birth injury, or long-term follow-up.

The 1 minute Apgar score is reduced in vaginal breech delivery.[1, 2] Kauppila[1] found, as expected, that the lowest Apgar scores occur in breech deliveries when the infants are injured by a traumatic delivery or when difficulty occurred during partial breech extraction. These factors should be avoided by cesarean section.

Most specialist units ensure that all breech deliveries are carried out in the presence of an experienced pediatrician immediately available to resuscitate the baby.

Birth injury may be increased during a vaginal breech delivery,[1, 3] but the injuries occur during difficult delivery. Extraction of a breech presentation by cesarean section may also cause birth injury.[3]

Long-term follow-up may fail to take into account factors other than breech presentation. Of special importance are prematurity and growth retardation, both of which seem to be more frequent in breech presentation.[1]

In assessing the role of cesarean section in breech delivery it is helpful to consider first the premature breech and then the mature breech, bearing in mind the fact that there is an excess of babies weighing less than 2,500 grams who have completed 35 weeks' gestation.

The premature breech. The perinatal mortality rate is higher in the premature breech than the premature vertex.[1, 2] Kauppila found that the perinatal death rate in single fetation breech deliveries was 38.7% in babies weighing 1,251 to 2,500 grams and 93.2% in babies weighing 601 to 1,250 grams. This compares with perinatal death rates of 19.5% and 80.1% in similar weight groups other than breech deliveries. These data refer to babies born between 1952 and 1961. Intrapartum deaths in small babies also occur more frequently during a vaginal breech delivery.[1, 5]

Thus it is established that premature vaginal breech delivery has a higher perinatal mortality rate and more intrapartum stillbirths than premature vertex delivery. It is not yet established that cesarean section can reduce this high perinatal loss.

The data of Goldenberg and Nelson[5] might suggest that the corrected perinatal mortality rate was marginally improved by cesarean section over vaginal breech delivery in very low-birth-weight infants (500 to 1,249 grams) but the numbers are too few for statistical analysis. Between 1,500 and 2,499 grams the perinatal mortality rate in babies delivered by cesarean section exceeded the perinatal mortality rate of vaginal breech delivery. This is the corrected figure which excludes major congenital abnormality. But congenital abnormality is more common in premature breech delivery,[1] so the uncorrected figure of perinatal deaths in premature babies delivered by cesarean section is higher still. Thus 4.2% of cesarean sections in premature babies resulted in delivery of a baby with a major congenital abnormality.[5] Goldenberg and Nelson suggested that a prospective evaluation of prophylactic cesarean section in unstressed breech presentation in infants under 1,500 grams is indicated. Such an approach is in our view contraindicated without first evaluating the present methods of intensive care in the premature breech labor.

Under optimal conditions the following management criteria should be followed: continuous fetal heart rate monitoring and fetal blood sampling from the buttock,[6] forceps to the aftercoming head,[7] continuous epidural or caudal anesthesia, an episiotomy, early vaginal examination to exclude cord prolapse, the avoidance of occipital diastasis due to hyperextension of the fetal head,[8] or manual pressure on the head via the abdomen. Intravenous dexamethasone in early labor is desirable, and skillful and immediate resuscitation at delivery is essential. The results of cesarean section in the premature breech must be compared to the above if any meaningful opinion is to result. There are, however, certain complications of premature breech delivery where the mortality and morbidity rates are so high that cesarean section is invariably justified. These include evidence of increasing asphyxia and prolapse of cord or hand.

The mature breech. As the cesarean section rate increases in mature breech presentations the perinatal mortality rate falls,[1, 2] so that the liberal use of cesarean section is indicated. In the two hospitals considered by Kauppila,[1] one had a cesarean section rate of 10.9% with a corrected perinatal mortality rate of 2.24%; the other had a cesarean section rate of 28.3% with a corrected perinatal mortality rate of 0.49%. Although cesarean section rates have increased with a corresponding drop in perinatal mortality rate, the rates reported by Kauppila would still be considered low by many standards, particularly in the United States. In our own series the total section rate was 21.9% and the total corrected perinatal mortality rate was 0.67% for all breeches. Since there is a general consensus that difficult breech delivery should be avoided because of the high fetal mortality and morbidity rates, cesarean section should be performed for a large baby and breech extractions must be avoided. Failure to progress in labor should be regarded as evidence of disproportion. Early fetal asphyxia, recognized by continuous fetal heart rate monitoring or buttock pH estimations,[6] should be treated by abdominal delivery. The flexed breech has a greater risk of prolapse of the umbilical cord[1] so consideration should be given to elective ce-

sarean section. Early recognition of prolapse of the umbilical cord is essential. Thus vaginal examination should be performed when the membranes rupture or when fetal dips appear on the electrocardiographic tracing. The mortality rate for cesarean section in cord prolapse is low.[9]

Cesarean section as a method of management of a complicated breech delivery obtains the best results in terms of fetal survival. There is, however, no information to suggest that extrapolation of incidence rates beyond 50% will further reduce the perinatal mortality rate. This information is required if the simple uncomplicated breech delivery is to be replaced by a major abdominal operation with the attendant increase in maternal morbidity and cost.

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GYNECOLOGY

Luteinizing hormone–releasing hormone levels in human plasma: A radioimmunoassay method

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A sensitive double-antibody radioimmunoassay, developed to measure luteinizing hormone–releasing hormone (LHRH) levels in fetal brain tissues, has been modified to quantitate LHRH in unextracted plasma samples. Pure, synthetic LHRH was iodinated with ^{125}I for tracer and was also used as standard. The antibody utilized was specific for LHRH and did not cross react with other hypothalamic or pituitary hormones. The separation of free from antibody-bound tracer was performed by dextran-coated charcoal. The sensitivity of the assay was 2.5 pg/tube. The intra-assay and interassay coefficients of variation were 5.9 and 6.1% for 50 pg/ml and 11.8 and 14.9% for 25 pg/ml samples. Recovery of known amounts of LHRH added to plasma samples that had no detectable hormone was 96.4 ± 8.8%. Whether these samples were previously prepared and kept frozen at −20° C or freshly prepared, the recovery of LHRH was consistent and quantitatively stable in each assay. Serial determinations of LHRH in plasma obtained from ovulatory volunteers averaged between 20.5 ± 2.1 pg/ml in the follicular phase and 19.4 ± 4.5 pg/ml in the luteal phase. At midcycle, coincident with the luteinizing hormone surge, LHRH levels averaged 17.6 ± 4.4 pg/ml. (AM. J. OBSTET. GYNECOL. 134:619, 1979.)

BY EMPLOYING invasive procedures into the hypothalamus, a luteinizing hormone–releasing hormone (LHRH) surge has been measured in the rat, rabbit, and rhesus monkey which has correlated well with a preovulatory LH surge.[1–3] Investigators have attempted to demonstrate similar findings in the human being and have measured LHRH in the peripheral plasma at midcycle by bioassays and radioimmunoassays.[4–7] Most of these involved laborious extraction procedures and required large volumes of plasma to measure this decapeptide produced in the hypothalamus and greatly diluted in the peripheral circulation. Some contradictory and inconsistent results have also been obtained.[8–10]

The quantitation of LHRH has posed many problems. Rapid inactivation by plasma enzymes, loss of immunoreactivity during processing of samples,[11, 12] and very low concentrations detected in plasma of women in the reproductive age[7, 8] have been reported. Investigators have been cautioned about the specificity of antibody used, iodination technique, and the cross-reactivity of tracer with serum proteins.[12, 13] This study was planned to measure LHRH in plasma samples of 10 normal ovulatory women during a complete menstrual cycle by a simple radioimmunoassay which has been modified from a sensitive, reproducible, double-antibody method developed to measure LHRH levels in the fetal hypothalamus.[14]

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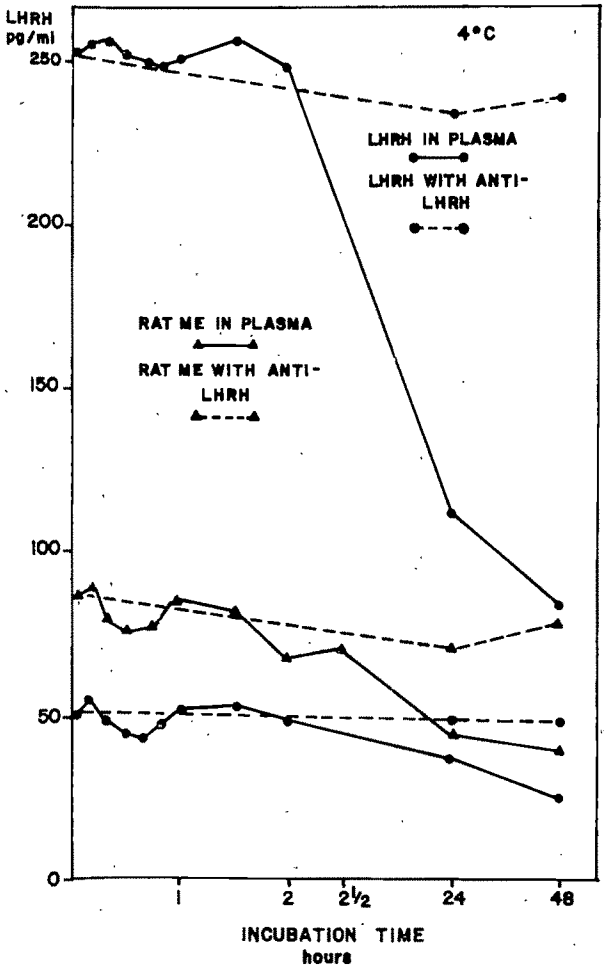


Fig. 1. Time course of plasma LHRH immunoreactivity at 4° C in comparison to LHRH values when samples were incubated with anti-1 LHRH.

Material and methods

Iodination. This method has been previously published.[14] The specific activity of the hormone obtained has varied between 52 and 76 μCi/μg. Labeling the hormone at a higher specific activity reduced its immunoreactivity. Tracer was repurified on a column (0.9 × 12 cm) of Sephadex G-25 prior to use for each radioimmunoassay.

Radioimmunoassay. Synthetic LHRH and tracer dilutions were made in phosphate-buffered saline (PBS) solution containing 1% gelatin at pH 6.5. The antisera was diluted in a solution of PBS containing 1/400 normal rabbit serum with EDTA and used at a working dilution of 1/100,000. The assay was conducted at 4° C and the reagents utilized were also kept at this temperature. Standards and samples contained 300 μl of buffer and 200 μl of plasma. The plasma utilized in standard tubes (0 plasma) was sterile, pooled, outdated, male plasma obtained from the blood bank, incubated at 22° C for several days, and recorded to have no LHRH activity after multiple extraction studies. Following a 24 hour incubation with 200 μl of antiserum (1/350,000 final dilution), 100 μl of LHRH tracer (150 pg) was added and incubation continued for another 24 hours. The separation of free and antibody-bound tracer was performed with the addition of ½ ml of ice-cold, dextran-coated charcoal suspension, prepared by adding 800 mg activated charcoal (Norit A-176) and 80 mg dextran T-70 to 100 ml of PBS, pH 6.5. A preliminary evaluation showed that 99% of unbound tracer could be removed in this manner. After centrifugation at 2,000 rpm at 4° C for 15 minutes, the supernatant was transferred to 12 by 75 mm plastic tubes by decanting, sealed with caps, and counted in a Beckman 310 gamma counter with a 70% counting efficiency, for 10 minutes or to 10,000 counts. Control tubes were routinely set up without antisera for determination of nonspecific binding for each assay.

Table I. Recovery of LHRH from heparinized blood

	Synthetic LHRH (100 pg/ml)		*Endogenous LHRH*	
Time (min.)	*4° C*	*22° C*	*4° C*	*22° C*
5	210.9	207.2	29.6	27.2
10	211.3	213.9	26.1	25.0
15	226.0	213.7	23.3	22.1
20	207.3	218.5	–	–
25	218.3	212.0	–	–
30	198.3	203.1	17.3	14.8
45	189.5	181.4	16.2	13.6

Collection of samples. Ten milliliters of heparinized blood was obtained by venipuncture from normal cyclic volunteers who had agreed to participate in the study and signed informed consent. The sample was spun within 10 minutes of withdrawal at 4° C. The plasma was separated into three aliquots, rapidly frozen, and kept at −20° C until assay. All samples from the same volunteer were run in the same assay. If a repeat run of a sample was necessary, an unthawed sample tube was used for the repeat LHRH determination.

Results

Stability of LHRH in heparinized blood and plasma. In view of temperature and time-related loss of LHRH activity in plasma,[11, 12] an appropriate method had to be devised for handling and storing of specimens prior to assay. The following experiments were performed to check the stability of LHRH in samples obtained with respect to time, temperature, and concentration.

Experiment 1: Stability of LHRH in blood specimens. To

Table II. Stability of LHRH in plasma

	Synthetic LHRH						*Rat ME extract*		
	50 pg/ml			*250 pg/ml*			*90 pg/ml*		
Time (min.)	*4° C*	*22° C*	*37° C*	*4° C*	*22° C*	*37° C*	*4° C*	*22° C*	*37° C*
Baseline	50.5			252.1			88.8		
5	50.1	50.0	43.0	256.1	253.0	250.8	90.3	86.9	86.4
10	55.1	47.6	44.2	269.3	267.7	265.4	92.6	87.1	85.9
20	48.0	44.1	47.8	256.0	270.0	247.0	82.3	87.2	85.0
30	45.0	46.8	51.6	253.5	247.0	237.5	78.2	91.8	80.6
40	45.2	50.2	40.9	252.1	240.3	233.0	83.7	85.1	77.8
60	54.0	50.1	41.0	252.0	243.2	247.3	90.1	75.7	73.7
90	57.0	50.3	33.6	261.9	232.2	219.1	85.9	79.0	64.7
120	–	–	–	–	–	–	73.2	73.9	57.3
150	–	–	–	–	–	–	75.1	65.8	49.5
1,440	39.5 (47.8*)	23.3	22.2	110.0 (251.6*)	40.9	28.4	47.5 (83.9*)	32.8	29.5
2,880	29.5 (48.7*)	22.8	25.9	84.1 (259.0*)	32.7	27.5	45.2 (82.9*)	30.7	28.4

ME = Median eminence.
*Incubation with antisera.

freshly drawn, heparinized, whole blood from a male volunteer (hematocrit 45%, baseline LHRH concentration 16.4 pg/ml), 100 pg. of synthetic LHRH was added per milliliter of blood. The blood sample was aliquoted into centrifuge tubes and half of the samples were kept at 4° C and the other half at 22° C. At 5, 10, 20, 30, and 45 minute intervals, the tubes were centrifuged at 4° C and the plasma was quickly frozen and kept at −20° C until assay. Heparinized blood was also obtained from a postmenopausal volunteer to evaluate the effects of delayed centrifugation on endogenous LHRH levels. After the samples were aliquoted into centrifuge tubes and kept at 4° and 22° C, respectively, they were centrifuged at 5, 15, 30, and 45 minutes. The results are shown in Table I. The endogenous LHRH decreased 20.9% and 18.9% from its baseline value at 4° and 22° C, respectively, when centrifugation was performed 15 minutes after the specimen was obtained. However, when the specimen was centrifuged 45 minutes later, there was a 45% and a 50% loss of immunoreactivity at 4° and 22° C, respectively. With a higher concentration of synthetic LHRH in heparinized blood, there was only 10.1% and 12.5% loss of immunoreactivity when the specimen was kept at 4° and 22° C for 45 minutes. Therefore, since the daily samples were expected to contain small concentrations of LHRH, the lab personnel strictly adhered to the rule of centrifugation of the blood specimen immediately after it was obtained.

Experiment 2: Stability of LHRH in plasma. Although the radioimmunoassay procedure was conducted at 4° C and completed within 48 hours, it was essential to determine if the LHRH levels remained stable during the preparation of the radioimmunoassay and during the incubation period. Table II shows the results of studies with 50 and 250 pg/ml concentrations of synthetic LHRH and rat median eminence extract diluted to 90 pg/ml concentration to be added to 0 plasma and incubated at 4, 22, and 37° C. Samples were rapidly frozen at 10 to 30 minute time intervals up to 2½ hours, then at 24 to 48 hour periods. Neither the synthetic LHRH nor the rat median eminence extract showed any significant decrease in LHRH immunoreactivity at 4° or 22° C within 90 minutes. The amount of decrease in LHRH activity appeared to be more pronounced at 37° C (Table II). However, when the 24 and 48 hour incubations were performed with the addition of antisera to the sample at 4° C, there was no loss of LHRH immunoreactivity (Fig. 1).

With these findings, the assay was carried out at 4° C. The addition of 0 plasma to the standard tubes and the addition of antisera to the assay were accomplished within 30 minutes. This alleviated the possible loss of immunoreactive LHRH during the preparation of the assay.

Experiment 3: Stability of LHRH in samples that were thawed and refrozen prior to assay. The LHRH value of a postmenopausal volunteer's plasma specimen was determined to be 55 pg/ml. This specimen was thawed and quick-frozen three times as aliquots for radioimmunoassay were obtained. The LHRH levels were as follows: first thaw, 53.6 pg/ml; second thaw, 46.5 pg/ml; and third thaw, 43.1 pg/ml. There was a 21% loss of measurable LHRH in the same sample if it was thawed for the third time. Therefore it was felt that if each plasma sample was aliquoted into three separate

Table III

Hormone	*Quantity (ng/tube)*	*Displacement*
LHRH	2.5	Complete
TRH	25.0	0
LH	25.0	0
FSH	25.0	0
Prolactin	25.0	0
Oxytocin	800.0	0

storage tubes, when a repeat radioimmunoassay was necessary, an unthawed specimen could be utilized to alleviate errors in measurement of LHRH.

Assay sensitivity and reliability. The assay sensitivity was 2.5 pg/tube. This amount of unlabeled LHRH produced an 8% to 10% fall in binding of tracer, whereas 2.5 ng. produced nearly complete displacement. Based on ten replicate samples containing 25 and 50 pg/ml of synthetic LHRH, the intra-assay coefficients of variation were 11.8% and 5.9%, respectively. The mean interassay variations of samples of similar concentrations in 12 different assays were 14.9% and 6.1%, respectively. Control samples utilized in each assay, containing physiologic and pharmacologic concentrations of LHRH, produced reproducible results in 25 assays. Whether these samples were freshly prepared for that particular assay or previously prepared and kept frozen at −20° C, the LHRH values were consistent and quantitatively stable in each assay.

The nonspecific binding of tracer was between 2.5% and 3%. The addition of plasma to assay buffer did not change the binding of tracer. In determination of maximum binding, the mean percentage bound was 69.5 ± 6.7 in 10 consecutive assays. This value was 15% higher than the mean percentage bound without the addition of 200 μl of 0 plasma which appeared to enhance antibody binding to tracer. On the curve, the point of 50% displacement varied between 52 and 58 pg/tube. The mean of the slope (least-squares linear regression of B/B^0 versus log dose of standard LHRH) in 10 consecutive assays was −2.52 ± 0.19.

Recovery of synthetic LHRH added to 0 plasma at 15, 25, 35, 50, 100, and 250 pg/ml concentration was 96.4% ± 8.8%.

Assay specificity. The curve generated by serial dilutions of rat median eminence extract in 0 plasma was parallel to the standard curve. Although 2.5 ng of LHRH produced almost complete displacement of tracer from antibody, there was no reaction with thyrotropin-releasing hormone (TRH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactin, and oxytocin, as shown in Table III.

Human plasma assay. LHRH concentrations in daily plasma of 10 normal ovulatory women during the follicular and luteal phases of the cycle varied between 10 and 35 pg/ml with a mean of 20.5 ± 2.1 pg/ml during the follicular phase and 19.4 ± 4.5 pg/ml during the luteal phase. Mean LHRH measured on the day of the LH surge in 10 samples was 17.6 ± 4.4 pg/ml.

Comment

Direct evidence for the existence of LHRH in the human peripheral circulation has provided the stimulus to many investigators to develop sensitive radioimmunoassays to quantitate the levels of this hypothalamic hormone. Reports have demonstrated that LHRH is more readily measurable in the postmenopausal than the perimenopausal women.[7, 15]

In view of the very small amounts of hormone detectable in the human plasma, many investigators have refined the assay sensitivity and cautioned the researchers about the pitfalls in measuring LHRH in the peripheral circulation.[8, 12, 13] A variety of extraction methods have been utilized to prevent the rapid degradation of this decapaptide in plasma but the recoveries have been problematic in the quantitation of the hormone.[4, 5, 7–9] In our laboratory, ethanol and methanol extractions using a 3 to 1 ratio have resulted in 25.6% to 44.2% recoveries, depending on the concentration of synthetic LHRH added to the sample. In view of the very small quantities of hormone present in the plasma samples, extraction procedures with small volumes of plasma will not yield significant results.

Enzyme inhibitors such as Trasylol or Benzamidine have been used to prevent degradation of LHRH in plasma.[9, 12] We have used Benzamidine in heparinized blood samples. When the plasma obtained was extracted, a higher level of LHRH was recorded in comparison to the sample without Benzamidine. Extraction of 0 plasma contaminated with Benzamidine at 0.005M or 0.01M concentration per milliliter demonstrated 25% and 45% displacement of tracer, respectively. Therefore, utilization of enzyme inhibitors ought to be evaluated for cross-reactivity with antisera.

Obtaining blood samples and centrifugation should be performed in a uniform and prompt manner. Since endogenous LHRH exists in such small quantities in plasma, there is rapid loss of immunoreactivity. Obtaining specimens for plasma rather than for serum allows for rapid centrifugation.

The data suggest that the addition of antisera to plasma samples at 4° C appears to protect LHRH from degradation in the specimens during a 48 hour incubation period, preventing loss of hormone activity in these samples. The iodinated tracer should be purified

prior to each use. The eluates with the lower specific activity recovered from the descending limb of the purification procedure have more immunoreactivity with the antibody, which is essential for assay sensitivity.

Determination of LHRH in normal ovulatory women does not appear to be of any clinical value. No specific pattern of LHRH concentration was observed in 10 normal menstrual cycles. During the day of the LH surge, no LHRH elevation was noted in 10 peripheral samples.

The synthetic LHRH and anti-LHRH were provided by W. C. Dermody, Ph.D., of Parke Davis & Company, Detroit, Michigan. The rat median eminence extract was provided by the National Institute of Arthritis, Metabolism, and Digestive Diseases, Bethesda, Maryland.

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Cellular and humoral immune status in women with chronic *Candida* vaginitis

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The cellular and humoral immune responses of nine women with chronic *Candida* vaginitis and 29 control subjects were evaluated. Agglutinating and precipitating antibodies were studied and tests of lymphocyte transformation, lymphokine production, and cutaneous delayed hypersensitivity were performed. The results suggest a lack of cellular immune response to *Candida* antigens in women with chronic *Candida* vaginitis. (AM. J. OBSTET. GYNECOL. 134:624, 1979.)

CANDIDA ALBICANS can be isolated from the vagina of approximately 16% of the nonpregnant female population of childbearing age.[1-3] The incidence of vaginitis due to this organism in the same population is approximately 6%[2, 4] or about 40% of women presenting with vaginitis.[5, 6] It is the most common infectious agent isolated from women attending venereal disease clinics.[3, 7]

The conversion of *C. albicans* from commensal to pathogen may be precipitated by a number of well-defined predisposing factors including pregnancy, diabetes, antibiotic or steroid therapy, antitrichomonal therapy, and iron-deficiency anemia. In addition, oral contraceptives have been incriminated as a cause of an increased indidence of *Candida* in the vagina[1, 3] and/or an increased incidence of *Candida* vaginitis among those harboring the yeast.[4, 8]

Recurrent vaginal candidiasis, a frequent sequel of a primary infection, may follow inadequate treatment or result from reinfection. Sources of reinfection are the patient's gastrointestinal tract[9] and the sexual partner.[10]

Impaired cellular immunity to *C. albicans* has been reported in patients with vaginal candidiasis. In studies of vaginal candidiasis in pregnancy[11] and in denture wearers with *Candida* denture stomatitis.[12] *Candida* infections were associated with a depressed cellular hypersensitivity to *Candida* antigens. While *C. albicans* readily induces a humoral antibody response, antibodies do not appear to offer any protection against current or subsequent infection.

The primary role of cell-mediated immunity in defense against *Candida* infections can be inferred from clinical data. Defective development or function of the thymus, endocrinopathies, leukemia, and immunosuppresive therapy are representative of conditions With concomitant defects in cellular immunity and frequent *Candida* infections.

The in vitro tests of cellular immunity most often performed are tests of lymphocyte transformation and lymphokine production, e.g., the testing of human lymphocytes for ability to produce leukocyte inhibition factor. These tests measure different aspects of the immune response. With these two tests and the in vivo test of cutaneous delayed hypersensitivity (skin test), the cellular immune status of a patient can be assessed. The goal of this cross-sectional study was to evaluate the cellular and humoral immune responses of women with chronic *Candida* vaginitis.

Material and methods

The subjects of this study attended the Gynecology Clinic of the Boston Hospital for Women or were seen

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in a private-practice setting between February and June of 1976. The patients were screened to rule out diabetes, pregnancy, steroid therapy, severe or debilitating disease, neoplasm, bilateral oophorectomy, and vaginal infections other than candidiasis (Table I). All patients were between the ages of 18 and 47. Twenty-nine control subjects were selected from women seen for yearly examination or for contraceptive measures (Group 1). Nine women who had chronic *Candida* vaginitis, i.e., more than three clinically diagnosed vaginal infections with *C. albicans*, were identified (Group 2). Criteria for the diagnosis of *Candida* vaginitis included irritating discharge and, on examination, reddening of the mucosa of the labia minora, the introitus, and the lower third of the vagina and the presence of white, lardlike patches. The diagnosis was confirmed by microscopic observation of the yeast or the mycelium or by isolation of the organism on modified Sabouraud's agar or on Mycosel prepared with 5% agar.

Specimens obtained at the time of the clinical examination included blood for complete blood count, dry swabs for mycologic examination from the middle third of the vaginal wall, wet swabs for mycologic examination taken from the rectum, wet swabs for microscopic examination taken from the vagina and examined immediately for trichomonad and yeast cells, and dry swabs for gonorrheal examination taken from the cervix. Women who were shown to be infected with *Trichomonas vaginalis or Neisseria gonorrhoeae* were excluded from the study.

Intradermal forearm injections of 0.1 ml of a 1:100 dilution of *C. albicans* 1:10 mold bulk extract (Hollister-Stier) and 40/10 U of streptokinase-streptodornase* were performed on all women. These tests were read at 48 hours. Induration of less than 5 mm was considered negative; 5 to 10 mm, intermediate; and greater than 10 mm, positive.

Lymphocyte transformation studies were performed on cells cultured by a modification of the procedure described by Chess and associates.[13, 14] The presence of leukocyte inhibition factor, as measured by its effect on the migration of leukocytes, was determined by a modification of a method developed by Castro and associates.[15]

Precipitating antibodies were detected by double immunodiffusion with the procedure of Murray and associates,[16] using a soluble yeast-phase antigen prepared as described by Syverson and associates.[17] Agglutinating antibodies were titrated by the method of Murray and Buckley,[18] using whole formalized *C. albicans* blastospores as the antigen.

*(SKSD) Varidase, Lederle Labs.

Table I. Potential confounding factors

Possible confounding factor	*Associated with*		*Method of control*
	Candidiasis	*Deficient cell-mediated immunity*	
Diabetes	Yes	Yes(?)	R
Pregnancy	Yes	Yes(?)	R
Iron-deficiency anemia	Yes(?)	Yes	N/A
Steroid therapy	Yes	Yes	R
Broad-spectrum antibiotic therapy	Yes	Yes(?)	N/A
Oral contraceptives	Yes	No(?)	A
Chronic disease	Yes	Yes	R
Neoplasm, malignancy	Yes	Yes	R
Alcoholism	Yes	Yes	N/A
Oophorectomy (complete)	Yes	?	R
Age	Yes	Yes	R
Other vaginal infections	?	?	R

R = Restriction (not permitted into study as case or control); A = analysis (upon completion of the study, factors labeled A were examined to see if they were, in fact, confounding); N/A = not present in any patient in this study.

Table II. Incidence of *C. albicans* isolation from vagina and rectum

Group	*Positive cultures for* C. albicans	*Site of positive culture*		
		Vagina	*Vagina/rectum*	*Rectum*
1 (29 cases)	3	3	0	0
2 (9 cases)	5	0	5	0

Results

Cultures. *C. albicans* was isolated from three of 29 control subjects (10%) and five of nine Group 2 women (55%). All positive cultures from the control subjects were from vaginal swabs while all of the infected patients had positive vaginal and rectal cultures (Table II).

Skin tests. The responses of the subjects to skin testing are shown in Table III. Intermediate and positive results to *C. albicans* antigens in Groups 1 and 2 totalled 50%, which is consistent with the observations of other authors.[12, 19] Three Group 2 women did not develop a positive skin test reaction to *C. albicans* despite a history of chronic *Candida* vaginitis. Intermediate and positive results in Groups 1 and 2 to SKSD equaled 31%.

Lymphocyte transformation test. The mean scintillation index (SI) values for the lymphocyte transformation test to *C. albicans* antigens are shown in Table IV. Results have been transformed to the log normal scale to normalize the distribution. The mean SI value for Group 1 was 6.67. There was a good correlation of skin test and lymphocyte transformation (Pearson cor-

Table III. Responses of subjects to skin testing with *Candida albicans* and SKSD

	Group 1	*Group 2*	*Total*
C. albicans			
≥10 mm	8 (28%)	5 (56%)	13 (34%)
5-10 mm	5 (17%)	1 (11%)	6 (16%)
<5 mm	16 (55%)	3 (33%)	19 (50%)
SKSD			
≥10 mm	7 (24%)	3 (33%)	10 (26%)
5-10 mm	1 (3%)	1 (11%)	2 (5%)
<5 mm	21 (72%)	5 (56%)	26 (68%)

Table IV. A summary of the scintillation index for lymphocyte transformation to *C. albicans*

Group	*Geometric mean*	*Confidence limits*	*Range*
1	6.67	5.31-8.38	1-116
2	7.27	4.49-11.77	1-118

Table V. A summary of the migration index of leukocyte inhibition tests of *C. albicans*

Group	*Mean and standard error*	*Range*
1	0.84 ± 0.06	1-0.61
2	0.81 ± 0.03	1-0.71

relation coefficient of 0.92) in this group. Although all members of Group 2 were chronically infected with *C. albicans*, the mean SI of this group was only 7.27 with a correlation coefficient of 0.61. No significant difference exists between the mean SI of Groups 1 and 2. No difference was observed between Groups 1 and 2 in the results of the lymphocyte transformation test to SKSD.

Leukocyte inhibition factor test. The mean migration index (MI) values of the leukocyte inhibition factor test for *C. albicans* are shown in Table V. No significant difference exists between the mean MI of Group 1 and Group 2. The Pearson correlation coefficients for the skin test and the leukocyte inhibition factor tests in Groups 1 and 2 were 0.62 and 0.59, respectively. No difference was observed between Groups 1 and 2 in the results of the leukocyte inhibition factor test for SKSD.

Antibody studies. None of the 29 women in Group 1 had precipitating or agglutinating antibodies to *C. albicans* detected in sera. Sera from four subjects (44%) in Group 2 had antibodies to *C. albicans*. Of these four sera, two contained agglutinating antibodies and two contained precipitating antibodies to this organism. The presence or absence of antibodies showed little correlation with skin tests or in vitro tests of cellular immunity in either the study or control groups.

Comment

The results of this study show that women with chronic *Candida* vaginitis cannot be consistently distinguished by four immunologic tests from women with no history of yeast infections. This implies either that the tests themselves cannot distinguish infected from uninfected patients or that women with chronic *Candida* vaginitis lack an immune response to *C. albicans*. The former assumption is probably false. The in vivo and in vitro tests of cellular immunity used in this study have been shown to become positive following active infections and to be specific in both animal models and human studies.[12, 20] Yet in this study of women with active infection the mean values for the skin test, the lymphocyte transformation test, and the leukocyte inhibition factor test did not differ significantly between infected and uninfected women.

In general, in vitro tests of cellular immunity show good correlation with the skin test in subjects previously exposed to the pathogen but without current disease.[19, 21] In a study of *Candida* denture stomatitis,[12] only nine of 29 patients with the disease reacted positively in a leukocyte migration test as compared to 25 of 28 skin test–positive patients without stomatitis. In the present study, a similar correlation is noted in that all 15 uninfected women with positive skin tests to *C. albicans* reacted positively to the leukocyte inhibition factor test, while of the nine women with chronic *Candida* vaginitis only three reacted positively in the lymphocyte transformation tests and four in the leukocyte inhibition factor tests. The observed discordance in infected women may be due to variable stimulation of the immune response, interaction of *C. albicans* or its products with components of the immune response, or inherent defects in the immune response of those women who develop chronic *Candida* vaginitis.

Oral contraceptives were associated with an increased incidence of *Candida* vaginitis (56% of Group 2 women were using oral contraceptives as compared to 28% of Group 1 women). However, no significant differences in the results of tests of cellular immunity were found among women using and not using oral contraceptives in Group 1. Dwyer and associates[19] reported a similar observation based upon comparison of skin tests and lymphocyte transformation tests in 40 healthy women. Thus, it appears that the use of oral contraceptives does not alter the immune response as measured by skin tests, lymphocyte transformation, or migration inhibition tests and thus, by definition, cannot be a confounding factor. However, the usage of oral contraceptives has been repeatedly associated with a higher than normal incidence of vaginal candidiasis.

The interaction of these agents with the vaginal microenvironment, e.g., epithelia, flora, secretions, and glucose content, may influence the extent and duration of colonization by *C. albicans*. This, in turn, should affect the immune response. The relationship between oral contraceptives, vaginal candidiasis, and the resultant immune response remains to be defined.

All of the chronically infected patients from whom yeast was isolated had yeast on rectal culture. Similar findings were recently reported by Miles and associates.[22] The high failure rate of many intravaginal therapeutic agents for vaginal candidiasis relates to these findings. The implication is that oral and vaginal therapy is indicated in chronically infected patients.

Resolution of infection with *C. albicans* has been associated with conversion from negative to positive results in tests of cellular immunity.[23, 24] A prospective study of women with chronic *Candida* vaginitis may show whether temporary eradication of infection through chemotherapy results in the development of positive responses to the in vivo and in vitro tests of cellular immunity. Such a study may detect fluctuations in the immune response which permits the conversion of *C. albicans* from commensal to pathogen or it may show that a depression of cellular immunity occurs only following an acute episode of *Candida* vaginitis. The present study suggests a lack of a cellular immune response to *Candida* antigens in women with chronic *Candida* vaginitis; the reasons for such chronicity remain to be elucidated.

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A randomized prospective study of the use-effectiveness of two methods of natural family planning: An interim report

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Data accumulated to date from the Los Angeles study indicate that the total termination rate for 12 months from the beginning of the training period and from formal entry into the study was high for the ovulation method (OM), and symptothermal method (STM). Voluntary withdrawal was the highest single reason for termination in both methods. The 12 month voluntary withdrawal rate, measured from formal entry into the study, was significantly higher for OM users. Pregnancy rates measured from both the beginning of training and formal entry into the study were significantly higher for OM users than for STM users. Complete analysis of the data collected during the study is currently in progress. It is anticipated that some of the causes for the differences in pregnancy rates and withdrawal rates between the two methods can be identified. (AM. J. OBSTET. GYNECOL. 134:628, 1979.)

THERE HAS BEEN a resurgence of interest in natural family planning. This may reflect increasing dissatisfaction with the adverse side effects of oral contraceptives and intrauterine contraceptive devices. "Natural" methods are devoid of the side effects associated with chemical and mechanical methods. Abstaining from genital contact during the fertile phase of the cycle is the basis of natural methods. Several methods have been used to determine the fertile and infertile phases of the menstrual cycle. These include calendar rhythm, basal body temperature, and cervical mucus observation. In the present study, the ovulation method (OM)[1–3] was compared to the symptothermal method (STM).[3–5]

The OM of natural family planning relies on observation of the cervical mucus pattern to identify the fertile phase of the menstrual cycle. Use of this method to avoid pregnancy requires abstinence during times of fertility. Sexual relations are permitted during the early preovulatory phase of the cycle up until the day on which mucus is first observed (vulvar sensation of wetness or lubrication). Abstinence begins on the first day of mucus secretion and continues until the evening of the fourth day past the "peak" or maximal mucus secretion. The "peak" mucus secretion occurs near the time of ovulation. Sexual relations are then permitted through the postovulatory phase of the cycle. Abstinence resumes at the onset of menses and continues until the period has subsided and reliable mucus observations are again possible.

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Table I. Number and characteristics of couples randomized, terminations during training, and entrants into study, by family planning method, Los Angeles study, August 31, 1978

Characteristics	*Total randomized*			*Terminations during training*			*Total entering study*		
	OM	*STM*	*Total*	*OM*	*STM*	*Total*	*OM*	*STM*	*Total*
No. of participants	404	434	838	218	212	430	186	222	408
Mean age of female partner	26.9	27.0	26.9	26.6	26.5	26.5	27.2	27.5	27.4
Mean age of male partner	30.0	29.5	29.7	29.6	28.9	29.3	30.4	30.0	30.2
Mean education of female partner	14.3	14.3	14.3	14.2	14.2	14.2	14.5	14.4	14.5
Mean education of male partner	15.1	15.0	15.0	15.1	14.8	14.9	15.2	15.1	15.1
Mean No. of living children	1.0	1.1	1.1	0.9	0.9	0.9	1.1	1.3	1.2
Mean years living together	4.4	4.6	4.5	4.2	4.2	4.2	4.6	4.9	4.8
Mean sex relations/month	10.9	11.1	11.0	11.6	11.5	11.6	10.1	10.7	10.4
Race of female (% white)	81	81	81	79	83	81	82	80	81
Religion of female (% Catholic)	47	54	50	40	46	43	54	60	58
Marital status (% married)	75	77	76	75	76	76	74	78	76

The STM of natural family planning employs not only cervical mucus observation but also a calendar calculation in the preovulatory phase and the basal body temperature shift in the postovulatory phase of the menstrual cycle to determine the time of fertility. The calendar calculation (21 is subtracted from the shortest cycle length in the preceding 6 months) establishes the last day on which sexual relations are permitted during the preovulatory phase. Abstinence begins before this day if mucus is noted. Abstinence continues until the third day of the basal body temperature rise. After this day, sexual relations may be resumed until the onset of menses.

From January 1, 1976, to August 31, 1978, 1,377 volunteer couples were enrolled in the study. The data presented were obtained from 838 couples who had (1) completed training, (2) dropped out of training, (3) dropped out of the study, and/or (4) completed 12 months of participation in the study. There were 539 couples in active training as of August 31, 1978; however, data from these couples were not included in this analysis but will be included in subsequent analysis. Eligibility criteria included: a stable couple relationship for at least 3 months prior to enrollment and a female partner between 20 and 39 years of age with menstrual intervals of 24 to 36 days. In addition, a normal history and physical examination of both partners and a negative pregnancy test were required. The couples gave a statement of motivation to avoid pregnancy, agreed to participate in the study for at least 12 months, and agreed to follow rules of the method assigned to them.

After informed consent was obtained, couples were randomly assigned to one of the two methods. Both partners were instructed in the use of the method by a professional teacher. The teachers were women who had previously used the method and/or had formalized training in teaching the method. The female partner met individually with her teacher, once per menstrual cycle, to review charting observations and proper use of the method. A serum or urine radioimmunoassay of the beta subunit of human chorionic gonadotropin was performed at each visit. Following a 3 to 5 month training phase, couples were formally entered into the study only if they had demonstrated proper use of the method.

After formal entry into the study, couples who violated the study protocol (missed appointments and/or occasional failure of abstinence) were allowed to continue in the study. However, couples who flagrantly violated the protocol (many missed appointments and multiple failures of abstinence) were dropped from the study. At the monthly clinic visits, couples who indicated that they were no longer interested in avoiding pregnancy were dropped from the study. Those who became pregnant were permitted to re-enter the study after termination of the pregnancy. All pregnancies occurring prior to formal dropout were included in the pregnancy rates. Pregnancies were categorized as

Table II. Net cumulative proportions of couples terminating during first year following the beginning of training period

Ordinal Month	Adjusted No. of women exposed		Reason for termination							
			All reasons		Pregnancy		Voluntary withdrawal		Other*	
	OM	STM	OM	STM	OM	STM	OM	STM	OM	STM
1	370.0	404.0	0.070	0.084	0.008	0.002	0.051	0.072	0.011	0.010
2	344.0	370.0	0.135	0.153	0.027	0.012	0.092	0.124	0.016	0.017
3	320.0	342.0	0.230	0.223	0.065	0.027	0.149	0.166	0.016	0.030
4	285.0	315.5	0.330	0.300	0.095	0.040	0.208	0.223	0.027	0.037
5	246.5	278.5	0.425	0.365	0.133	0.062	0.254	0.248	0.038	0.055
6	209.5	244.5	0.480	0.430	0.155	0.073	0.287	0.295	0.038	0.062
7	188.0	212.5	0.541	0.484	0.166	0.086	0.332	0.335	0.043	0.063
8	161.5	186.0	0.609	0.539	0.188	0.094	0.366	0.368	0.055	0.077
9	130.5	157.5	0.651	0.586	0.206	0.094	0.384	0.415	0.061	0.077
10	109.5	129.5	0.686	0.612	0.222	0.101	0.400	0.431	0.064	0.080
11	91.0	106.5	0.727	0.630	0.229	0.112	0.434	0.435	0.064	0.085
12	70.0	87.5	0.759	0.647	0.229	0.112	0.461	0.447	0.069	0.088

*Includes involuntary terminations, moved, and lost to follow-up.

Table III. Net cumulative proportions of couples terminating during first year following formal entry into study

Ordinal month	Adjusted No. of women exposed		Reason for termination							
			All reasons		Pregnancy		Voluntary withdrawal		Other*	
	OM	STM	OM	STM	OM	STM	OM	STM	OM	STM
1	185.5	219.5	0.027	0.009	0.005	—	0.011	—	0.011	0.009
2	177.0	211.5	0.087	0.051	0.033	0.005	0.043	0.023	0.011	0.023
3	160.5	193.0	0.150	0.096	0.056	0.019	0.072	0.033	0.022	0.044
4	142.5	173.5	0.257	0.163	0.097	0.051	0.120	0.059	0.040	0.053
5	119.0	153.0	0.295	0.223	0.122	0.056	0.132	0.103	0.041	0.064
6	110.0	132.5	0.391	0.270	0.154	0.056	0.171	0.144	0.066	0.070
7	89.5	114.0	0.432	0.302	0.161	0.063	0.198	0.163	0.073	0.076
8	78.5	98.5	0.526	0.338	0.197	0.084	0.256	0.177	0.073	0.077
9	59.0	82.5	0.550	0.346	0.197	0.084	0.280	0.185	0.073	0.077
10	49.5	73.5	0.623	0.390	0.216	0.084	0.334	0.221	0.073	0.085
11	38.0	62.0	0.653	0.430	0.226	0.094	0.354	0.251	0.073	0.085
12	31.0	50.5	0.697	0.452	0.248	0.094	0.366	0.262	0.083	0.096

*Includes involuntary terminations, moved, and lost to follow-up.

either method failures or user failures. Method failures were those pregnancies judged to be due to an inherent deficiency in the method (i.e., a pregnancy occurred despite apparent proper use of the method). All other pregnancies were categorized as user failures. Six method failures and 48 user failures occurred during the formal study period. Seventy-eight pregnancies occurred during the training period. In this analysis, however, all pregnancies are grouped into a single category.

Table I summarizes some of the pertinent characteristics of randomized couples. Generally, the couples tended to be sexually active and in their late 20's, have a small family and a high educational level, and be predominantly white.

Couples dropping out during the training period tended to be younger than couples completing training and entering the study. Also, they had lived together a shorter period of time, were more active sexually, and had fewer children and a lower educational attainment than the couples who completed training. Less than half of the couples randomized completed training and entered the study.

The cumulative probabilities of termination for various causes during the first year following the beginning of training and the first year following formal entry

into the study were analyzed. These data are summarized in Tables II and III. The life-table method employed is a modification of the approach described by Potter.[6]

In the preparation of life tables, allowance was made for four types of decrement: pregnancy, voluntary withdrawal, involuntary termination, and moved away or lost to follow-up. The voluntary withdrawal group included couples who dropped out because of lack of interest or dissatisfaction with the method, desire for pregnancy, relationship ended, vaginal discharge or difficulty with mucus identification, menstrual irregularity, and/or miscellaneous other reasons. Cumulative proportions of couples terminating for these reasons during the first year following the beginning of training are shown in Table II. The involuntary withdrawal and lost to follow-up groups were combined because of the relatively small numbers involved. At the end of the first year following enrollment in training, the life-table cumulative termination rate for all causes was 75.9% for OM couples and 64.7% for STM couples.

Voluntary withdrawal accounted for the highest proportion of terminations in each method (46.1% for OM and 44.7% for STM). Pregnancy was the next highest, with 22.9% of OM (SE = 2.21) and 11.2% of STM couples (SE = 1.65) terminating for that reason. This difference in pregnancy rates is highly significant.*

Cumulative proportions of couples terminating during the first year following formal entry into the study are shown in Table III. The 12 month life-table cumulative rate for all causes was 69.7% among OM couples and 45.2% among STM couples. Voluntary withdrawals accounted for the highest proportions in each of the two groups—36.6% of OM users (SE = 3.74) and 26.2% of STM couples (SE = 3.35). The pregnancy rate was 24.8% among OM users (SE = 3.93) and 9.4% among STM users (SE = 2.33). These differences between methods in pregnancy rates and in voluntary withdrawal rates are significant; however, the number of women exposed during ordinal months 7 through 12 was less than 100.

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*The test statistic used was $z = (P_1 - P_2)/[(SE)_1^2 + (SE)_2^2]^{1/2}$ where P_1 and P_2 are cumulative pregnancy rates of the two groups and SEs are standard errors of the respective cumulative pregnancy rates.

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Human chorionic gonadotropin β-subunit–like immunoreactive material in the plasma of women wearing an intrauterine progesterone contraceptive system

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A systematic study of the presence of human chorionic gonadotropin β-subunit–like (hCGβ-like) material in the plasma of one woman sampled daily throughout one menstrual cycle and in nine women studied on a selected bleeding schedule has been carried out. Peaks of immunoreactive hCGβ-like activity were found in the follicular and luteal phases of these menstrual cycles which could not be explained by a cross-reaction of luteinizing hormone (LH) in the plasma. The same nine women were studied again 1 month after the insertion of the intrauterine progesterone contraceptive system (IPCS) and again 6 to 8 months later. Although the presence of hCGβ-like immunoactivity correlated with LH values in the cycles studied, there was a significant decrease in its presence 1 month after IPCS use and a highly significant decrease after 6 to 8 months of use. (AM. J. OBSTET. GYNECOL. 134:632, 1979.)

IT HAS BEEN suggested that approximately 12% to 19% of women wearing an intrauterine contraceptive device (IUD) become transiently pregnant, a prediction based on elevated human chorionic gonadotropin β-subunit–like (hCGβ-like) material in the plasma of these women.[1] The endocrine changes in women wearing the intrauterine progesterone contraceptive system (IPCS) have been studied in some detail by Bryant-Greenwood and associates.[2] It was shown that ovulation occurred in all the cycles studied despite significantly elevated levels of plasma estradiol-17β and decreased levels of prolactin and relaxin immunoactivities by the sixth to eighth month of follow-up.

The purpose of this study was to determine whether any of these same nine women were covertly or transiently "pregnant" after insertion of the IPCS, that is, whether fertilization occurred without subsequent implantation as judged by a specific radioimmunoassay for hCG when applied to these plasma samples.

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Material and methods

Radioimmunoassay for hCG β-subunit. Highly purified hCG (Serono), radioimmunoassay potency 6,100 IU/mg, was used for labeling with I^{125} by the chloramine T method of Hunter and Greenwood.

The antiserum of hCG β-subunit was from rabbit No. 1 and a gift from Drs. Kosasa and Taymor.

Since it is anticipated that only low levels of hCG might be detectable in these "early pregnancy" cycles an assay was developed for maximum sensitivity. Standard hCG, 0.2 ml of solutions containing 800, 400, 200, 100, 50, 25, 12.5, 6.25, and 3.1 pg/ml in a 1:2 dilution of horse serum (Grand Island Biological Company) in 0.05M barbitone buffer, pH 8.6, was used, or plasma (0.2 ml) of eight dilutions from 1:4 to 1:512 in 1:2 horse serum in barbitone buffer was added to polystyrene incubation tubes (6 by 1 cm, Luckhams Ltd.). Antiserum to hCG β-subunit (0.05 ml of 1:7,000 dilution in barbitone buffer, pH 8.6) was added to each tube.

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Table I. Interassay variability of the standard curve over a 4 month period

Amounts of hCG (Serono) (pg/ml)	*% Bound (N = 8)*
800	2.2 ± 0.66
400	2.8 ± 0.85
200	3.7 ± 0.51
100	8.8 ± 1.88
50	13.3 ± 3.02
25	18.3 ± 3.14
12.5	20.0 ± 4.36
6.25	19.0 ± 3.14
3.1	23.0 ± 4.86

Table II. Precision of the assay

Concentration range of hCG β-subunit (pg/ml of plasma)	*Estimated SD (s)*
50-100	±25.2 (16)
100-200	±25.4 (13)
200-500	±41.4 (19)
500-2,000	±111.6 (7)

Different samples of plasma were assayed at three convenient dilutions. The numbers of assays at three concentrations of plasma are given in parentheses. Values of s, an estimate of the standard deviation, are calculated in terms of picograms of hCG β-subunit per milliliter of plasma. The mean calculations of hCG β-subunit in the plasma samples obtained are grouped into the concentration ranges shown.

The tubes were mixed gently, capped, and incubated at 4° C for 72 hours prior to the addition of ^{125}I-labeled hCG (50 pg in 0.05 ml of diluent). Diluent refers to a solution of 0.5 mg/ml bovine gamma globulin, Fraction II (Nutritional Biochemical Corporation). Each tube was again gently mixed, capped, and returned to 4° C for a further 72 hours' incubation. Separation of bound and free hormone was carried out by a conventional double-antibody procedure. To each tube was added 0.05 ml normal rabbit serum, 1:20 dilution, in barbitone buffer, pH 8.6, 0.05M, and 0.1 ml sheep anti rabbit gamma globulin in barbitone buffer containing 370 mg/100 ml ethylenediamine tetraacetate (EDTA). The tubes were mixed gently, recapped, and replaced at 4° C for 24 hours. Separation was achieved by centrifugation in a refrigerated Sorvall RC-2 at 2,000 g, the supernatants were carefully decanted, and the precipitates were counted in a Packard Autogamma counter. Percentage bound was calculated (counts bound/counts bound + free) and plotted against amounts of standard or plasma used.

Precision and sensitivity of assay in routine use. Plasma levels varied over a wide range such that a single quality control sample was not appropriate for the calculation of interassay and intra-assay variation. We have used a log linear plot of amounts of hCG against

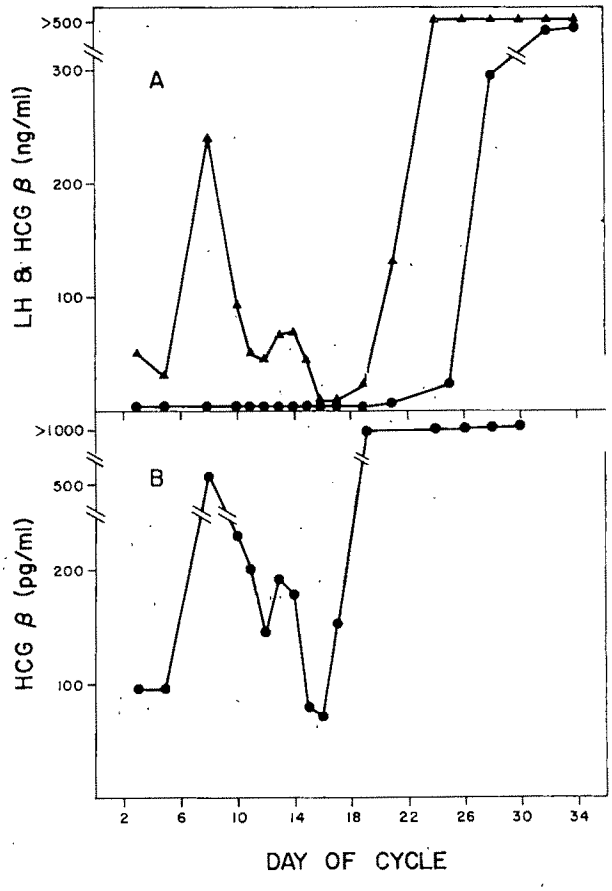


Fig. 1. Pregnancy cycle. *A:* hCG β-subunit assay data (●——●) plotted on the same scale as the LH values (▲——▲). *B:* hCG β-subunit assay data (●——●) plotted on a scale consistent with the maximal sensitivity of the assay. Note that levels after day 19 become increasingly greater than 1,000 pg/ml.

the percentage of labeled hCG bound to antibody and fitted the best straight line over the range 200 to 3.1 pg/ml hCG to give the between-assay variability of the standard curve over 4 months (Table I). In addition the precision of the assay when applied routinely to the measurements of hCG β-subunit in plasma has been calculated (Table II) as follows. Estimations were routinely carried out at six dilutions such that a minimum of three points could then be used to check parallelism between the unknown and standard. From a series of such assays at three concentrations of plasma the precision of the method in practice was calculated as shown in Table II. The quantitative sensitivity of the method was 25 pg/ml or 0.15 mIU hCG β-subunit/ml plasma as calculated from the first drop in the standard curve.

Cross-reactions. LER 907 cross reacted in the assay such that 400 pg of hCG (Serono) was equivalent to 1 μg of LER 907. These results are identical to those published by Vaitukaitis and colleagues.[3]

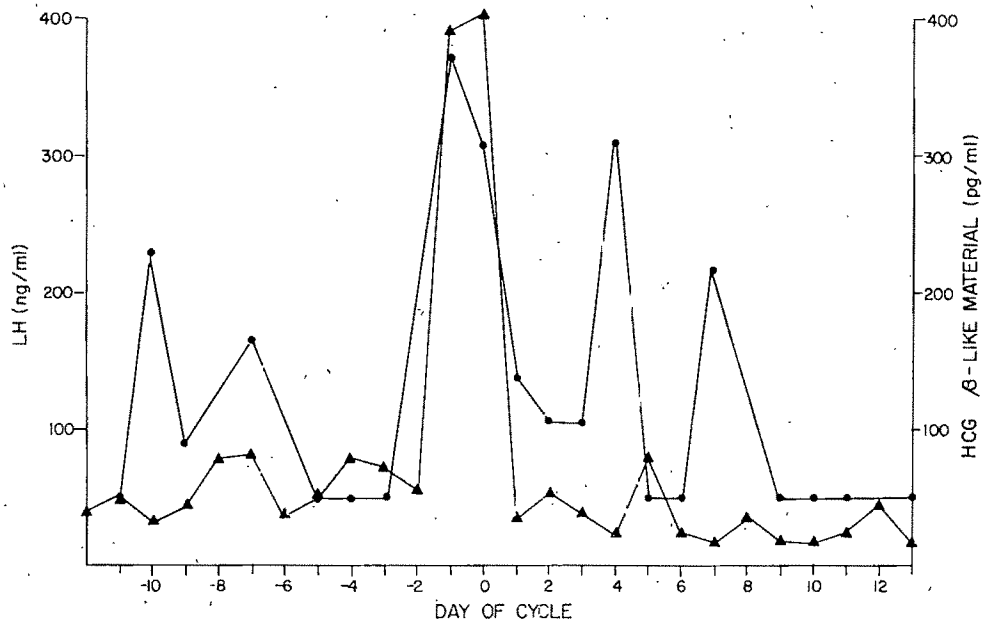


Fig. 2. LH (▲——▲) and hCGβ-like immunoactivity (●——●) in a normal woman from whom samples were taken daily for one menstrual cycle.

Radioimmunoassay for LH. Human luteinizing hormone (LH) (LER 907 for the standard and LER 960 for iodination) and antiserum No. 1 were provided by the National Pituitary Agency. The assay has been previously described by Odell and associates.[4] The sensitivity was such that 31.3 ng or 1.5 mIU LER 907/ml plasma could be differentiated from zero.

Sample collections. The samples were identical to those studied for LH, follicle-stimulating hormone (FSH), estradiol-17β, progesterone, prolactin, and relaxin immunoactivities.[2]

Nine healthy women (22 to 28 years) were selected for this study with each subject acting as her own control. None had any history of dysmenorrhea, none had received hormone therapy or oral contraceptive pills for at least 3 months prior to the study, and each had spontaneously menstruated at least once subsequent to the withdrawal of hormones. In addition blood samples from one normal healthy woman with a normal menstrual cycle were obtained daily for 36 days; these data were not included in the analysis of the control study for the women wearing the IPCS.

In the control cycles, blood samples were obtained at the start of menstruation and on days 5, 9, 11, 13, 14 to 17, 19, 21, 25, and 29 and then each day until menstruation. The IPCS was inserted between 1 and 5 days after the onset of menses. Blood samples were collected starting on the day of menstruation and on days 5, 10, 12, 14, 16, 18, 20, 22, 25, 27, and 29 and then every other day until menstruation for the first menstrual cycle (N = 9) and again at 6 to 8 months after the insertion of the IPCS (N = 8). One of the subjects left Hawaii prior to the 6 month follow-up. Blood was collected by venipuncture at 0900 hours ± 20 minutes in order to minimize any possible diurnal variation.

One subject subjectively reported a heavier than normal menstrual flow, while another subject had a milder than normal flow at the first month of the IPCS; the remaining subjects experienced no change. These two subjects reverted to their normal menstrual flow pattern by the sixth month. Seven subjects experienced intracycle spotting during the first month with the IPCS, whereas only two experienced any spotting by the sixth month.

One subject in the control cycle became overtly pregnant and was therefore a useful positive control cycle for this hCG β-subunit study.

Results

hCG β-subunit material in early pregnancy. One subject's control cycle, which was subsequently dropped from the overall study, was a pregnancy cycle. This showed an LH peak on day 8 of the cycle followed by a smaller LH peak on day 14 (Fig. 1, *A*). When the hCG β-subunit assay was plotted on the same scale as the LH values (Fig. 1, *A*) conventional results were obtained, showing a rise in hCG levels by day 28. However, when the hCG β-subunit results were plotted on a

scale consistent with the maximal sensitivity of the assay (Fig. 1, *B*) it can be seen that the hCG β-subunit assay reflects the physiologic levels of LH prior to ovulation and to day 16.

All of these plasma samples diluted out parallel to the standard as would be expected from their LH content. However, plasma samples from days 3, 5, 15, and 16 were not parallel and were toward the lower limits of sensitivity for the assay. The lack of parallelism at low levels suggests the assay is detecting material related to LH or hCG or derived therefrom. By day 17, hCG β-subunit levels were parallel to the hCG standard and thereafter rose dramatically and were greater than 1,000 pg/ml by day 19, in concert with the results of the LH assay (Fig. 1, *A*).

hCG β-subunit material in nonpregnant cycles. LH and hCGβ-like material were assayed in daily samples from a normally cycling woman (Fig. 2). It can be seen that over the midcycle LH peak the hCG β-subunit assay clearly measured LH; however, there were four peaks of immunoactivity at −10, −7, +4, and +7 days which cannot be explained simply on the basis that LH cross reacted in the hCG β-subunit radioimmunoassay (40 pg hCG ≡ 100 ng LH).

A more detailed study was therefore carried out on nine normal women from whom samples were taken on days 5, 9, 11, 13, 14 to 17, 19, 21, 25, and 29 and then each day until menstruation. The results were combined according to the day of the LH peak, thereby aligning the rest of the results. The standard error of the mean was calculated by logarithm transforms for each day of the cycle and were too small to plot (Fig. 3, *A*). Peaks of hCGβ-like material appeared again on days −10, −9, −5, −4, −3, +5, +12, and +14 which cannot be explained by cross-reactivity with endogenous LH alone. It was considered to be of interest to see whether for the entire control cycle the hCGβ-like activity would relate to LH activity; hence when the correlation coefficient for these two variables is used (r = 0.76) this is a significant correlation.

When the data for the first month after insertion of the IPCS in these women were treated in a manner identical to those of the control cycles, a very similar result was obtained (Fig. 3, *B*). However, hCGβ-like material in the follicular phase on days −10 and −6 and in the luteal phase at day +3 was again apparent but to a lesser extent. This immunoactivity throughout the cycle correlated significantly with LH values on the same samples (r = 0.92). When the 6 to 8 month samples were treated similarly and plotted, the midcycle LH peak was markedly lower than that of either the control cycles or the first month after IPCS insertion

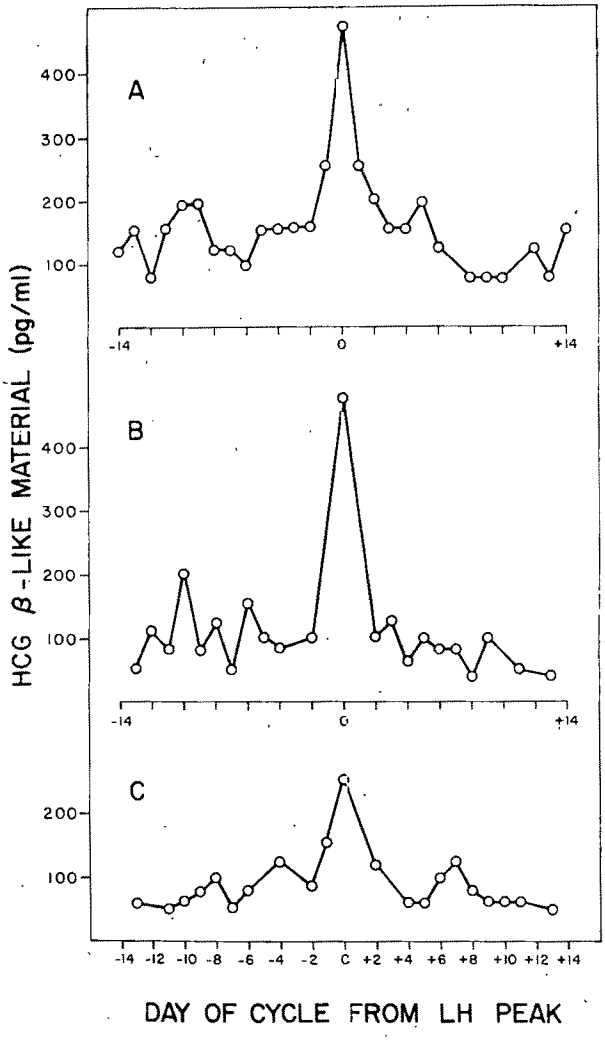


Fig. 3. hCGβ-like immunoactivity. *A:* Normal menstrual cycle (n = 9). *B:* One month after insertion of the IPCS (n = 9). *C:* six to eight months later (n = 8). Data were combined for each series according to the day of the LH peak. The standard error of the mean of logarithm transforms was calculated but was too small to be plotted.

cycles (Fig. 3, *C*).[2] Again hCGβ-like immunoactivity for the whole cycle correlated significantly with the LH levels (r = 0.62).

The overall level of hCGβ-like activity was compared in the control and first month after insertion of the IPCS cycles by Student's t test. There was significantly less hCGβ-like activity when the IUD was in use ($P < 0.01$). When the overall levels were compared between the control cycles and the 6 to 8 month follow-up there was a very highly significant reduction in hCGβ-like immunoactivity ($P < 0.001$). There was no significant decrease between the first and 6 to 8 month follow-up levels with IPCS use ($P > 0.05$).

It has been shown that in the same samples LH val-

ues did not significantly change at either 1 month or 6 to 8 months after IPCS use.[2]

Comment

This is the first systematic study of hCGβ-like immunoactivity throughout the normal menstrual cycle and on subsequent use of an IUD.

An extensive discussion on overall cycle lengths and follicular and luteal phase lengths in the cycles of the subjects studied has already been published.[2] Likewise it has already been shown that in the same samples the only significant change with use of the IPCS for 6 to 8 months that occurred was an increase in estradiol-17β levels ($P < 0.05$). No significant change in either LH or FSH levels were recorded.[2] Hence, although the hCGβ-like substance measured in this study correlated well with plasma LH values previously recorded, this correlation does not preclude an overall significant fall in hCGβ-like levels.

A similar study has been carried out using an hCG β-subunit radioimmunoassay as well as a radioreceptor assay on women wearing a copper IUD.[1] The results of this study showed 12% to 19% of IUD users with hCG in the serum during the luteal phase of the cycles. This suggests that with the copper IUD the women became covertly "pregnant" and had a fertilized ovum up to the implantation stage which was capable of secreting small amounts of hCGβ-like activity. Hence the copper probably causes interference through degeneration of the blastocyst and consequent lack of implantation.

From our study of nine women wearing the IPCS we have shown hCGβ-like immunoactivity decreased with up to 6 to 8 months of use rather than increased as was our a priori expectation. A significant fall has been recorded from the control cycles to the first month of IPCS use and an even more significant fall between the control cycles and those after 6 to 8 months of IPCS use. This suggests that the presence of intrauterine progesterone acts differently as a contraceptive agent than does copper. Indeed one study on the mechanism of action of the IPCS shows that at least part of its action is due to a direct capacitation-inhibiting effect of the uterine secretion[5]; hence fertilization would not occur and hCG β-subunit levels would not be elevated by the presence of a blastocyst. It is, however, difficult to explain why hCG β-subunit levels should actually show a decrease with IPCS use.

The immunoactive material measured here by the sensitive hCG β-subunit radioimmunoassay is of interest since we have shown its presence in normal cycles. Its presence has been reported by other workers. It has been demonstrated that such a chorionic gonadotropin, normally secreted by cytotrophoblast and syncytiotrophoblast of the placenta, can be secreted into blood by tumors developed from these cell types and by teratomas of the ovary, testis, or pineal, by hepatoblastomas, and by 6% to 13% of carcinomas of the lung, stomach, pancreas, and colon.[6-8] It has also been shown that extracts of normal human testis contained such a substance.[8] Evidence has been published for the presence of a substance in urinary extracts of normal, nonpregnant subjects of possible pituitary origin,[10] and more recently it has been shown that the liver and colon of normal subjects may elaborate a chorionic gonadotropin, akin to hCG, albeit without a carbohydrate moiety.[11] The results reported here in the blood of normal subjects are in agreement with these urine and tissue studies.

Peaks of immunoreactive hCGβ-like material have been shown to be present in both the follicular and luteal phases of the normal menstrual cycle. This cannot be explained on the basis of cross-reacting endogenous LH where cross-reactivity is calculated on the basis of purified standard LH in the hCG β-subunit radioimmunoassay. Clearly endogenous LH in plasma may not behave in the same manner since metabolic products of LH would probably also inhibit the hCG β-subunit system. Hence a spectrum of immunoreactive LH in plasma is probably measured. If this were the case one explanation of the decrease in hCGβ-like activity with IPCS use would be an altered metabolism of LH.

Irrespective of the origin of this plasma immunoactivity related to the subunit of hCG β-subunit throughout the menstrual cycle and its physiologic significance to the cycle, it may be inferred from its very ubiquity that the material gives no evidence for the presence of covert pregnancies in subjects wearing the IPCS system. Indeed the effect of the latter is to reduce the levels under the circumstances with no known physiologic sequelae.

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Increased platelet aggregation and decreased high-density lipoprotein cholesterol in women on oral contraceptives

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In vivo platelet function, serum total cholesterol (TC), high-density lipoprotein cholesterol (HDL), and serum triglycerides (TG) were determined in 26 women starting oral contraceptives (OCA). Studies were run prior to, and after one and two months of therapy. Platelet aggregation time decreased by 50 percent or more in eight of the 26 women from a pre-experimental mean value of 387 ± 136 seconds. TC did not vary but after the women were on medication for two months, HDL decreased from 56 ± 14.4 mg/dl to 52 ± 12.3 mg/dl ($p < 0.05$). There was a progressive increase in TG under treatment, 74 ± 23.3 mg/dl on the pre-experimental measurement to 93 ± 31.0 mg/dl after two months of therapy ($p < 0.005$). Women planning to use OCA might best be advised to have aggregation and serum lipid studies done before and early in usage. (AM. J. OBSTET. GYNECOL. 134:638, 1979.)

MANY epidemiologic studies have shown a marked relationship between use of oral contraceptives and an increased incidence of myocardial infarction, stroke, and thrombophlebitis. This was particularly marked among women who smoke. A recent report[1] suggested that a shift of cholesterol from the alpha fraction to the beta compartment might be the mechanism responsible for these conditions. Earlier workers[2] had not noted a relationship between serum cholesterol and stroke, and related phenomena. In a pilot study several years ago in this laboratory, several young women on oral contraceptives were noted to have marked platelet hyperaggregability as measured by the Filtragometer[3] technique, one shortly after initiating therapy. Since it appeared likely that platelet hyperaggregability played a major role in oral contraceptive complications, both platelet aggregation and lipids were measured in a prospective study over a period of two months in an attempt to delineate possible mechanisms.

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Methods

Twenty-six women, aged 18 to 45 years, who were about to begin therapy with oral contraceptives in a large community-based obstetrics and gynecological practice, formed the cohort for the study. At the initial visit to the practice, in addition to the usual medical care, they were studied by means of the following tests.

1. Platelet aggregability as measured by the Filtragometer technique was done as follows.[3] The aggregation of platelets in flowing blood was assessed by drawing blood via an indwelling polyethylene cannula

Table I. Effect of oral contraceptives on in vivo platelet function in women

Women	*Aggregation time (sec.)*		
	Pre-experimental	*Month 1*	*Month 2*
All women on OCA (N = 26)	358.8 ± 162.9*	366.7 ± 168.4	437.6 ± 156.9
Control women not on OCA (N = 18)	267.4 ± 142.4	291.3 ± 166.9	
Women on OCA who had <50% decrease (N = 8)	386.9 ± 135.5	155.1 ± 68.9†	355.3 ± 232.8
Women who had a < 50% decrease after one month and remained on contraceptive for Month 2 (N = 5)	457.2 ± 70.9	172.4 ± 76.4†	209.8 ± 145.4
Women who had a <50% decrease and went off contraceptive on Month 2 (N = 3)	269.7 ± 145.7	126.3 ± 54.6	597.7 ± 79.5†

*Mean ± standard deviation.
†$p < 0.01$.

from an antecubital vein through a microfilter of 20 μm pore size into a motor-driven syringe, at a constant rate of 2.0 dl per minute. This filtration method is based on the use of a pore size which permits passage of red and white blood cells and platelets but is occluded by platelet aggregates. The system was maintained at 37° C. in a heating block. Heparin was infused into the system proximal to the filter at an anticoagulant concentration of 5 units per deciliter of blood. The system proximal to and including the filter was siliconized. Pressure was monitored proximal and distal to the filter, the rise in pressure difference reflecting occlusion of the filter by aggregated platelets. Macroscopic inspection and scanning electron microscopy of the filter confirmed the presence of aggregated platelets and the absence of blood clot. The procedure has been found to be reproducible. The pressure gradient across the filter was recorded for periods of up to ten minutes. The aggregation time (number of seconds taken to reach a gradient of 5 mm Hg) was noted and recorded.

2. Lipid profile to include serum cholesterol, cholesterol in the high-density lipoprotein fraction, and serum triglyceride fatty acid pattern was done.

3. Complete blood count with differential was done.

The women then were started on their assigned medication containing 1 mg norethindrone and 0.05 mg ethinyl estradiol and returned three weeks after beginning to take their medication. This was on average some three to four weeks after they were initially seen. At that time, a repeat series of studies was performed and those who developed major abnormalities of any of the parameters were advised to discontinue the medication. All subjects in the cohort were restudied a third time one month later whether they were on or off therapy to study either the cumulative effects of the contraceptives or pattern of normalization after therapy was discontinued. All subjects were advised to avoid aspirin for 10 days prior to being studied and not to smoke for at least two hours before the visit because of the confounding effects on platelet aggregation.[4, 5] They were also briefly interviewed prior to initiation of therapy by a nutritionist to obtain a brief diet history in the form of a 24 hour recall. The diet material was then tabulated and calculated for varying amounts of calories, cholesterol, saturated fat, and linoleate from the appropriate tables. The subjects were then advised to adhere to the same pattern for the ensuing two months since any radical increase in dietary linoleate might significantly alter aggregation time.[6]

Any complications were noted and all vital data was provided to the treating physicians to aid in the overall management of the subjects. Data analysis was done by the two-tailed paired Student t test.

Results

The effect of oral contraceptive agents on in vivo platelet function in the cohort studied is shown in Table I. As a group, the 26 patients showed no statistically significant change in aggregation time during the two-month period of observation. The trend was essentially the same as that noted for 18 age-matched control subjects not on oral contraceptives studied at a one-month interval. However, 8 of the 26 women on the oral contraceptive agents did show greater than a 50% drop in aggregation time during the two-month period of observation going from 387 seconds to 155 seconds at one month ($p < 0.01$) and then 355 seconds at two months largely because of the tremendous rebound toward normalcy of the three women discontinuing therapy after one month. This three-women subset changed from 270 seconds to 126 seconds at one month and then rebounded to 598 seconds ($p < 0.01$) on cessation of drug for one month. The remaining five sensitive subjects decreased from 457 seconds to 172 seconds at one month ($p < 0.01$) and stayed essentially unchanged while they were on the drug at two months.

The serum lipid changes for the entire 26 person

Table II. Effect of oral contraceptive pills on serum lipids in women

	Pre-experimental	*Month 1*	*Month 2*
Serum cholesterol (mg/dl)	170.3 ± 35.5*	160.4 ± 19.7	166.7 ± 24.1
High-density lipoprotein cholesterol (mg/dl)	56.6 ± 14.4	58.4 ± 15.5	51.8 ± 12.3†
Serum triglycerides (mg/dl)	72.9 ± 22.0	83.3 ± 29.7†	92.9 ± 31.0‡

*Mean ± standard deviation.
†$p < 0.05$.
‡$p < 0.01$.

Table III. Effect of oral contraceptives on in vivo platelet function in women

	Pre-experimental	*Month 1*	*Month 2*
Women who had a decrease in A.T. (N = 8)			
Aggregation time (sec.)	387 ± 136*	155 ± 69†	355 ± 233
	Individual values		
Women who had a decrease in A.T. and HDL (N = 2)	402	104	
Aggregation time (sec.)	460	226	
High-density lipoprotein	58	48	
Cholesterol mg/dl (N = 2)	69	45	

*Mean ± standard deviation.
†$p < 0.01$.

chohort are shown in Table II. The serum cholesterol stayed essentially unchanged mirroring the unchanged fat content of the diet consumed during the two months. However, the high-density lipoprotein cholestrol did change from 56.6 mg/dl to 51.8 mg/dl in two months and this decrease was significant ($p < 0.05$). The same was true for the serum triglycerides which increased significantly as early as one month (72.9 to 83.3 mg/dl; $p < 0.05$) and further increased to 92.9 mg/dl ($p < 0.01$) at the two-month mark.

Table III takes a closer look at the eight women who had a 50% or greater decrease in aggregation time in an attempt to delineate those who had adverse concomitant changes in aggregation and HDL cholesterol. There were two such women with observed changes altering what are considered "safe" to high-risk category levels (i.e., aggregation time <250 seconds and high-density lipoprotein cholesterol <50 mg/dl). One other subject in this group had stable but abnormally low HDL cholesterol and with her greater than 50% decrease in aggregation time she was considered to be in the high-risk category.

Comment

In late 1977 two major prospective studies on the influence of oral contraceptives on the health of users were reported.[7, 8] Both groups found an increased mortality rate from diseases of the circulatory system in oral contraceptive users, confirming the results of earlier retrospective studies. The Royal College of General Practitioners study[7] again noted the adverse effects of age and smoking but in addition noted a significant risk of cerebrovascular accident among users over nonusers. This further substantiated the reports of Horenstein[9, 10] showing a relationship of stroke and related phenomena to oral contraceptive use and raised considerable question as to the mechanisms involved in these processes.

Hennekens[11] had reported that oral contraceptive use over a 3 year period led to increased serum cholesterol and triglyceride levels and suggested that this might be the mechanism for increased risk of coronary heart disease. The report of Wallace and associates[12] substantiated these findings biochemically in ten diverse North American population groups. However, no explanation was set forth for the other complications noted such as stroke, transient ischemic attack, thrombophlebitis, or headache.

In exploring the pathogenesis of atherosclerosis, Ross and Glomset[13] cited the important role of abnormal platelet activity along with that of smooth muscle proliferation and abnormal lipid levels. A subsequent review of the entire matter[14] added the observation that abnormal serum lipids, per se, increased platelet hyperaggregability and further complicated the attempt to sort out etiologic factors. Work in this laboratory[5, 15, 16] had shown a clearcut relationship between platelet hyperaggregability, per se, and acute and chronic coronary heart disease, stroke, smoking, and stress among other factors. Interestingly, most of these factors have been found to increase risk of oral contraceptive use by the Royal College of General Practitioners study group.

The data in this study showed no significant total

serum cholesterol changes after oral contraceptives were used for two months. It did, however, show a significant drop in HDL cholesterol and rise in serum triglycerides during the interval. Since so much has been written about the importance of the serum cholesterol level over prolonged periods of time in producing atherosclerosis, some questions must be raised as to the unilateral role of this factor in producing disease in so short a time in this young cohort. More important, 8 out of the 26 (31%) subjects studied here had a 50% or greater drop in platelet aggregation time bringing them into risk factor range for vascular complications in general in the two-month period. Three of this subset also had abnormal HDL cholesterol levels providing the appropriate background for the future development of atherosclerosis. Of course, all eight were advised against use of the oral contraceptives, but should continued usage prove necessary, they serially might be monitored with the above parameters at regular intervals.

These data are still preliminary but show the value of early evaluation of platelet aggregation activity and serum lipids in those starting and continuing oral contraceptive agents. Further studies seem appropriate to confirm these findings, with a view to screening out those who can not tolerate these agents before any cardiovascular complications develop.

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Human hexosaminidase isozymes

IV. Effects of oral contraceptive steroids on serum hexosaminidase activity

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Data from a mass screening program for identification of persons who are heterozygous for Tay-Sachs disease have been analyzed for the effects of oral contraceptive steroids on the activity in serum of hexosaminidase (hex) and the various hex isozymes. Women using oral contraceptives show a significantly higher total serum hex activity, reflecting mainly an increase in the heat-stable hex isozyme (hex I), and a smaller increase in the heat-labile hex A than do women using no medications. The changes in women using oral contraceptives are qualitatively similar to those observed during pregnancy. The distribution of responses to oral contraceptives is unimodal, and some of the variations may be related to differences in amount of steroid ingested. In addition, underlying genetic variation may contribute to the observed differences in enzyme activities.
(AM. J. OBSTET. GYNECOL. 134:642, 1979.)

A DECREASE in activity of N-acetyl-β-D-hexosaminidase (hex) in serum,[1] other body fluids and secretions,[2] and tissues[3] has been utilized in the identification of the heterozygous person or carrier of the Tay-Sachs gene. In addition to problems of interpretation encountered when values for hex A activity fall in the inconclusive range between noncarriers and persons who are obligate heterozygotes, false positive results are uniformly observed with the thermal inactivation procedure for fractionation of the hex isozymes during pregnancy.[4] Similarly, tests on patients with diabetes mellitus and other disorders may give false positive results.[1]

In the original description of the carrier detection method, O'Brien and associates[1] noted that women using oral contraceptive steroids may give false positive test results. A later report by other investigators suggested no differences in hex activity between normal women and women on low-dose oral contraceptives.[5] More recently, however, an increase in activity of serum hex and β-glucuronidase was observed in women on various regimens of oral contraceptives. Moreover, there appeared to be a direct correlation between the dose of steroid ingested and the increase in hex activity.[6]

During the course of a community mass screening program for Tay-Sachs carrier detection, in which more than 8,000 persons were tested by assay of hex activity of serum samples, we had the opportunity to determine the effects of oral contraceptive steroids and other medications on activity of the enzyme. The purpose of this report is to summarize our findings and to confirm the effects of oral contraceptives in producing changes in serum hex activity that resemble qualitatively those observed during pregnancy.

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Method of procedure

Subjects. The mass screening program began in 1972 and was initiated for the purpose of identifying

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Tay-Sachs heterozygous individuals among persons of childbearing age, i.e., 18 to 45, in the Jewish community residing in the New York City Metropolitan area and in several upper New York State communities. The Tay-Sachs carrier test was offered on a voluntary basis, following efforts to inform and educate the target population in accordance with procedures employed in earlier mass testing programs in other communities.[7]

At the time of the screening, persons volunteering for the test were registered and completed a questionnaire to provide identifying data, information relating to current and previous health status, use of medications according to a check list of specific types of drugs, and answers to questions bearing on knowledge or information about the screening program and attitudes relating to prevention or control of genetic disorders. At the time of registration, persons having the test were assigned one of a series of consecutive numbers, and analysis of the results and the questionnaire data were carried out by the assigned number, thereby assuring anonymity of the person tested.

For the purpose of this study, questionnaires completed during eight consecutive screenings in the community were reviewed. Noncarrier women were assigned to one of four groups, including those who were not taking any medication, women receiving medications other than oral contraceptive steroids, such as tranquilizers, antihistamines, or analgesics, women using oral contraceptive steroids only, and women using oral contraceptives in addition to other medications. The distribution of subjects in the various groups is summarized in Table I, where it can be seen that information relating to 1,129 women between the ages of 15 and 48 years was reviewed. Approximately 58% of the women were receiving no medications at the time of testing, and the remainder were on a regimen of oral contraceptives or other medications or a combination of both. Detailed analysis of the findings is restricted to two groups: (1) 652 healthy noncarrier women receiving no medications, and (2) 128 healthy noncarrier women using oral contraceptive steroids but no other medication. Women identified as carriers or who fell in the inconclusive group and were not available for additional studies to clarify their status were not included in this analysis.

The data from the questionnaire were transcribed on summary sheets that were used for key punching on IBM cards. Data storage and analysis were carried out with the aid of a Xerox Sigma 6 computer. The information utilized for this study includes age of the subject, health status, current use and type of medications employed, and results of the serum hex assay, including total activity and absolute and relative activities of the heat-labile (hex A) and the heat-stable components (hex B and I).



Fig. 1. Age distribution of women using oral contraceptive steroids and no medication.

Table I. Distribution of population sample

Group	*No. of women*	*% of sample*
No medications	652	57.8
Oral contraceptive steroids	128	11.3
Other medications	295	26.1
Oral contraceptives and other medications	54	4.8
Totals	1,129	100

Methods.

Serum hexosaminidase. For mass screening, hex A is fractionated by the thermal inactivation method.[1] Serum samples are diluted 10 times with 10 mM phosphate/6.3 mM citrate buffer (pH 4.4) and inactivated for 2 and 3 hours in a constant temperature circulating water bath at 52° C. Enzyme activities in the control and heated samples are assayed using a Technicon AutoAnalyzer II according to methods described elsewhere.[8] Activity of total hex and the heat-labile and heat-stable isozymes is expressed as nanomoles of 4-methylumbelliferone (4MU) released per 0.1 ml serum per 8 minutes. The hex components are also expressed as a proportion or percentage of total activity.

For clarification of inconclusive results or confirmation of the carrier state, alternative methods are used. These include a column chromatographic separation of the hex isozymes, using a diethylaminoethyl (DEAE) cellulose column and subsequent assay of the individual fractions using the AutoAnalyzer.[8] Alternatively, repeat blood specimens are obtained using siliconized Vacutainer tubes containing 0.2M citrate for

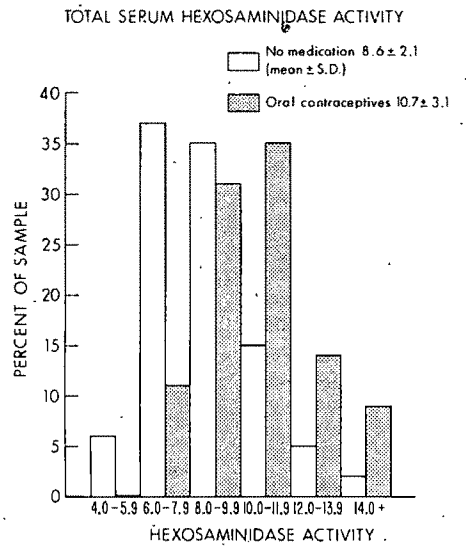


Fig. 2. Total serum hexosaminidase activity in women using oral contraceptive steroids and no medication.

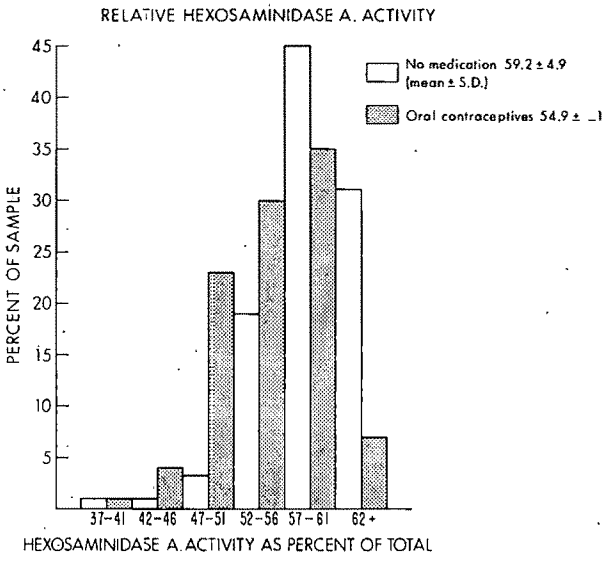


Fig. 3. Relative activity of hexosaminidase A, as a percentage of total hexosaminidase, in serum of women using oral contraceptive steroids and those receiving no medication.

separation of blood platelets. Assay of the individual hex isozymes in platelet extracts after fractionation by a DEAE-cellulose microcolumn is done with the Auto-Analyzer according to a procedure described elsewhere.[9]

Results

The age distribution of women using oral contraceptive steroids or receiving no medications is shown in Fig. 1. The distribution of ages for the oral contraceptive group is unimodal, with a mean and standard deviation of 26.4 ± 4.3 years. In contrast, there is a shift to older ages among women receiving no medication, where the mean and standard deviation are 29.2 ± 6.7 years. There is an apparent bimodality because of the grouping of women 34 years of age and older. Of the women using no medication 31% were in this age category, in contrast to only 5% of women using oral contraceptives. There is a statistically significant difference between these groups in regard to age distribution ($t = 4.548$, $p < 0.001$), which is not surprising because of recent demographic studies of patterns of oral contraceptive use.[10]

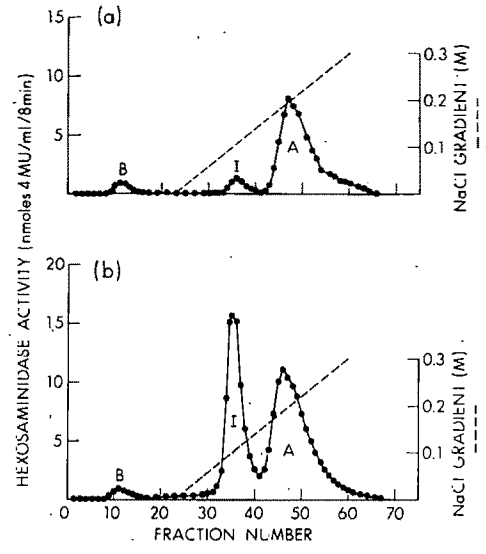


Fig. 4. Distribution of the hexosaminidase isozymes in serum from a woman receiving no medication *(a)* and from a woman using oral contraceptive steroids *(b)*. The hexosaminidase isozymes in these samples were fractionated by DEAE-cellulose chromatography as described in "Methods." Enzyme activity is expressed as nanomoles of 4MU released per milliliter of eluate per 8 minutes.

The distribution of total serum hex activity is shown in Fig. 2. There is a statistically significant difference between the mean values for women using no medication (8.6 ± 2.1, mean ± SD) and the women using oral contraceptive steroids (10.7 ± 3.1, $t = 9.367$, $p < 0.001$). The distribution of values for total serum hex of women using oral contraceptives is unimodal, with a general shift to higher activities and no indication of polymorphism in this response.

The increase in total serum hex activity of women using oral contraceptive steroids is reflected in a similar statistically significant increase in activity of both hex A and B isozymes, although the absolute magnitude of the increment is greater for hex B (Table II). As a result of the differential increase in activity of the hex isozymes, there is a significantly lower relative activity

Table II. Summary of findings in women using oral contraceptive steroids or receiving no medications

Finding	*Group*		*Statistical evaluation*	
	No medications	*Oral contraceptives*	*t*	*p*
Age (yr.)	29.2 ± 6.69*	26.4 ± 4.29	4.548	<0.001
Total serum hex (nm. 4 MU/0.1 ml/8 min.)	8.6 ± 2.13	10.7 ± 3.14	9.367	<0.001
Hex A	5.0 ± 0.97	5.8 ± 1.22	7.912	<0.001
Hex B	3.6 ± 1.31	5.0 ± 2.17	9.602	<0.001
A (%)	59.2 ± 4.94	54.9 ± 5.09	8.856	<0.001
Serum cholesterol (mg/dl)	184 ± 35.9	190 ± 33.6	1.486	NS
Serum triglycerides (mg/dl)	53 ± 29.8	80 ± 37.2	7.390	<0.001

NS = Not significant.
*Mean ± S.D.

Table III. Activity of serum hexosaminidase isozymes fractionated by DEAE-cellulose chromatography

Group	*Hexosaminidase activity**			
	A	*I*	*B*	*A (%)*
Noncarriers (N = 21)	78.6 ± 10.2†	16.4 ± 6.4	3.4 ± 1.5	80 ± 5.8
Noncarriers using oral contraceptive steroids (N = 5)	84.9 ± 6.9	40.5 ± 8.9	6.2 ± 2.4	65 ± 4.7

N = number of subjects.
*Nanomoles 4MU released/8 min./1.5 ml serum.
†Mean ± SD.

of hex A, expressed as a percentage of total activity, in women using oral contraceptives (Fig. 3).

Although the activity of serum hex has been alluded to in terms of the activities of the A and B isozymes, in fact, the thermal inactivation method for fractionation of these components in serum identifies heat-labile and heat-stable hex activity at 52° C and pH 4.4. Studies by other investigators as well as ourselves have shown that the heat-stable activity includes activity of several hex components other than the B isozyme.[8] When the hex isozymes in serum of women using oral contraceptives or receiving no medications are fractionated by chromatography on DEAE-cellulose, the differences illustrated in Fig. 4 and summarized in Table III are observed. Although there is some increase in activity of hex B in serum of women using oral contraceptives, a more important contribution to the change in activity of the heat-stable hex fraction is an increase in activity of hex I. This is a heat-stable component present in the serum of normal persons, that increases considerably in activity in patients with Tay-Sachs disease and in persons who are heterozygous for Tay-Sachs disease. A chromatographically indistinguishable component with similar thermal stability properties increases dramatically during pregnancy and has been termed hex P.[4] The terms hex P and hex I are used interchangeably since there is no method available to distinguish between these isozymes. Indeed, they may be identical in molecular structure as well as kinetic and physicochemical properties. Thus, the changes in serum hex activity of women using oral contraceptive steroids reflect mainly an increase in hex I and qualitatively resemble the alterations observed during normal pregnancy.

Comment

The results of this study confirm and extend previous reports of an effect of oral contraceptive steroids on total activity in serum of hex and the activity of the various hex isozymes.[1, 6] These changes are characterized by an increase in total serum hex activity, reflecting an increase in the heat-labile isozyme, hex A, and a more marked increment in the activity of the heat-stable form of the enzyme. In contrast to previous reports that have attributed this change to an increase in hex B, chromatographic methods for fractionation of the hex isozymes demonstrate that the change is mainly due to an increase in hex I, another heat-stable isozyme. As a result of these changes, the relative activity of hex A, expressed as a percentage of total activity, is decreased and, in some instances, may fall in the inconclusive range or suggest the carrier state for the Tay-Sachs gene.

An analysis of the basis of the variation in activity of hex and its component isozymes in serum from persons tested in the course of a mass community screening program has shown a statistically significant regression

of hex activity on age, with higher activities in older individuals.[11] Although the age distribution of women using oral contraceptive steroids showed a statistically significant trend to younger ages in comparison with women receiving no medication, the distribution of activities of hex and the heat-labile and heat-stable molecular forms of the enzyme in the group using contraceptives showed significantly higher values, contrary to the expectation from the age differences observed.

Although the data have not been presented, women receiving medications other than oral contraceptive steroids, such as tranquilizers, antihistamines, or analgesic drugs, showed no significant alterations of serum hex activity compared with the findings in women receiving no medication.

Although various types of oral contraceptives were used, information about dose or duration of use was too fragmentary to permit evaluation of a possible dose-response relation between oral contraceptive steroid intake and change in serum hex activity. However, a preliminary report indicates that the increase in activity of total serum hex as well as serum β-glucuronidase is related to total dose of estrogen and progesterone ingested.[6] This may be a major factor in the observed variation of increase in hex activity in serum of women using oral contraceptive steroids. Studies are in progress to assess this response. In addition to variations in steroid dose, it is possible that some of the differences in hex activity in response to oral contraceptives may reflect underlying genetic variation and further studies may aid in clarifying this possibility.

The changes in serum hex activity resemble qualitatively the alterations observed in women during pregnancy, when there is an increase in total serum hex, reflecting a striking increase in hex P, a heat-stable isozyme indistinguishable by currently available methods from hex I, and a less pronounced increase in hex A.[4, 8] The changes observed during pregnancy may be unique for serum, since studies of enzyme activity in peripheral blood leukocytes,[12] platelets,[9] and other tissues, including placental and fetal tissues, have not revealed similar alterations.[4, 13] Indirect evidence, related to increases of serum hex activity associated with hepatitis,[5] and observations in serum and perfused liver preparations from experimental rats with streptozotocin-induced diabetes mellitus[14] suggests that liver is a major source of various serum lysosomal hydrolases, including the hex isozymes.

Assay of serum hex activity is a convenient and practical method for Tay-Sachs carrier identification.[1] However, alterations associated with use of oral contraceptive steroids, pregnancy, or various disorders such as diabetes mellitus, may yield inconclusive or false positive results. Alternative methods may be necessary to accurately distinguish carriers from noncarriers and to confirm the carrier state ascertained by thermal inactivation of serum samples. Electrophoretic and chromatographic methods for fractionation of the hex isozymes can be employed for these purposes using serum or cell and tissue extracts. The greater complexity and longer time required for these alternative techniques may preclude their use as primary methods for carrier identification during mass screening programs. However, they may be useful and important adjuncts for more precise identification or confirmation of the Tay-Sachs carrier state, particularly during pregnancy.

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Hypothalamic-pituitary responses to high concentrations of gonadal steroids in a three-month-old infant with a feminizing gonadal stromal tumor

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A 3-month-old female infant feminized by an ovarian stromal tumor is presented. Clinicopathologic aspects of such tumors occurring in infancy are discussed. In addition, the evaluation of hypothalamic-pituitary function preoperatively and postoperatively are presented. In the preoperative, high-steroid environment, both basal and stimulated secretion of follicle-stimulating hormone (FSH) was suppressed. Secretion of luteinizing hormone (LH) was normal. Following surgical castration, stimulated secretion of both gonadotropins clearly increased. These findings suggest an active but less sensitive negative feedback mechanism for FSH than for LH during infancy, i.e., high concentrations of gonadal steroids are necessary to maximally suppress FSH secretion while normal steroid concentrations appear to maximally suppress LH secretion. Developmental changes in hypothalamic-pituitary sensitivity to negative feedback controls are discussed in light of these findings. (AM. J. OBSTET. GYNECOL. 134:648, 1979.)

FEMINIZING OVARIAN TUMORS occur in both adults and children. Although approximately 5% of these tumors occur in children,[1] they are distinctly uncommon in infancy. Active secretion of gonadal steroids by these tumors may cause precocious sexual development. Maturational changes of the hypothalamic-pituitary-ovarian (HPO) axis, however, are absent. The increased steroid concentration in such cases presents an unusual opportunity to examine functional aspects of the HPO axis. Such investigations might be expected to add to the limited information now available on function of the HPO axis in infancy. This study of a 3-month-old infant with a feminizing ovarian tumor examines hypothalamic-pituitary function in both a high- and low-steroid environment.

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Case study

The patient, a female infant, was delivered at term following an uncomplicated prenatal course. The neonatal course was normal; however, the infant was hospitalized at 3 months of age with lobar pneumonia. Bilateral breast tissue was palpable at this time and the abdomen was slightly protuberant. The pneumonia resolved with standard therapy. At 3½ months of age, bleeding through the vagina occurred. Both the breast tissue and abdominal distention were more prominent and an evaluation was initiated.

On admission the pulse was 164 beats per minute and respirations were 70 per minute. Blood pressure and temperature were normal. The weight was 7.33 kg (ninetieth percentile) and the length was 61 cm (fiftieth

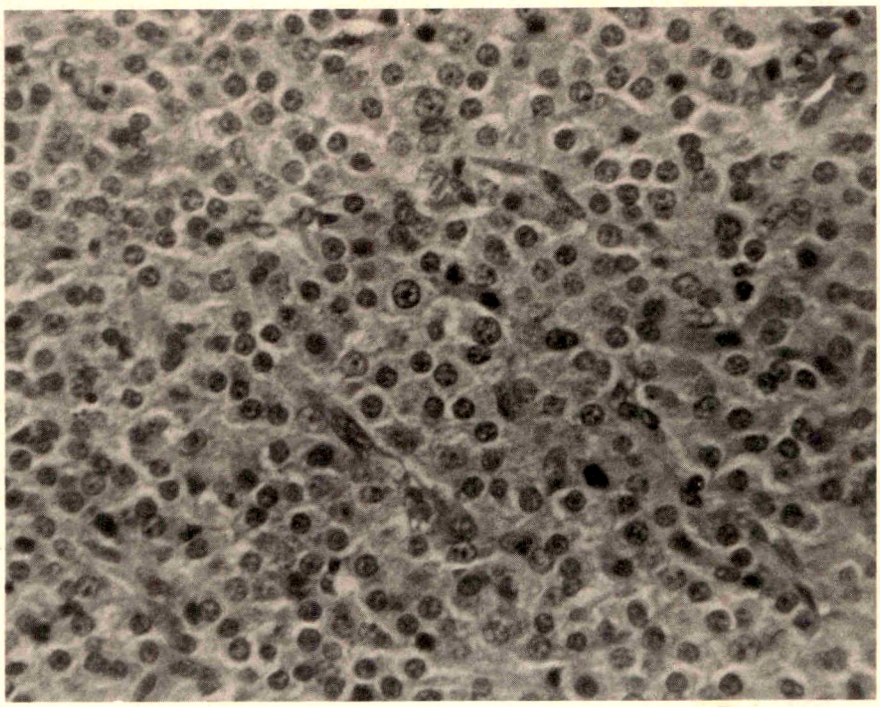


Fig. 1. Marked luteinization of the tumor is present. Call-Exner bodies are absent. (Hematoxylin and eosin. ×250.)

percentile). The abdomen was distended with a girth of 51 cm. Breast tissue was palpable, approximately 5 cm in diameter bilaterally, and the areolae were darkened. The remainder of the examination, including rectopelvic and cardiovascular parameters, was normal. Increasing respiratory distress over the next 2 days was relieved by abdominal paracentesis.

Laboratory values obtained on admission were as follows: hematocrit, 39%; white blood cell count, 19,000/mm^3; blood urea nitrogen, 30 mg/100 ml; total protein, 5.5 g/100 ml; albumin, 3.1 g/100 ml; creatinine, 0.8 mg/100 ml; total bilirubin, 0.4 mg/100 ml; lactic dehydrogenase, 190 mU/ml; and serum glutamic oxalacetic transaminase, 35 mU/ml. Urinalysis, including a pregnancy test, was normal. Ascitic fluid was yellow and clear, with a specific gravity of 1.024 and a total protein of 3.2 g/100 ml. No malignant cells were noted on cytologic examination, and bacterial cultures were negative. Both intravenous pyelography and liver-spleen scan, except for ascites, were normal.

Examination during anesthesia revealed a pelvic mass and laparotomy was undertaken. Clear ascitic fluid, 1,500 ml, was evacuated and the abdomen was inspected. An encapsulated, yellow, 5 cm, solid tumor replaced the left ovary and was removed. The remainder of the pelvis appeared normal. The right ovary was less than 1 cm in length and no irregularities were palpated. No lymph nodes were palpable and the liver and peritoneal surfaces were normal. Postoperatively the patient did well. The serum 17β-estradiol fell rapidly from a preoperative level of 4,980 to 59 pg/ml by the third postoperative day.

Two months following operation the serum 17β-estradiol concentration rose to 898 pg/ml and bleeding through the vagina again occurred. On examination the breat tissue was unchanged and the areolae were more pigmented. An enlarged cervix and uterine corpus were palpable on rectoabdominal examination. Both the height and weight were greater than the ninetieth percentile for the patient's age. Routine laboratory studies were normal and the chest x-ray film and abdominal ultrasonography were unremarkable. Intravenous pyelography indicated a mass displacing the bladder. The liver-spleen scan was normal. Examination during anesthesia revealed a 3 cm mass palpable in the area of the right adnexa. A second laparotomy revealed a 3 cm, solid, yellow tumor of the remaining right ovary. Total hysterectomy and right salpingo-oophorectomy were performed without difficulty. Thorough inspection of the abdomen and liver failed to reveal further evidence of tumor. Postoperatively the patient did well and is clinically free of recurrence at one year. The 17β-estradiol concentration has remained less than 50 pg/ml.

Material and methods

All blood samples were obtained by single venipuncture or by indwelling intravenous needle. The serum was separated and stored at −20° C until ana-

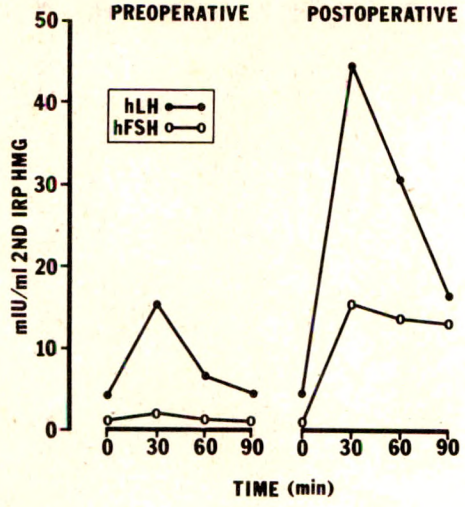


Fig. 2. LH-RH, 50 μg, was injected intravenously at time 0 on both occasions. The responses of both gonadotropins were increased postoperatively, i.e., following surgical castration ($p < 0.05$). *2nd IRP HMG* = Second International Reference Preparation of human menopausal gonadotropins.

Table I. Preoperative and postoperative concentrations of gonadal steroids

	Steroid		
Time	*Progesterone (ng/ml)*	*Estrone (pg/ml)*	*Estradiol (pg/ml)*
Preoperative:	13.1	1,328	4,979
Serum	13.1	1,328	4,979
Ascites	11.6	1,167	3,475
Postoperative:			
Day 3	0.2	47	59
Day 7	0.3	34	70

lyzed. Ascitic fluid was also frozen for subsequent analysis. The poor status of the infant prior to the original operation precluded extensive endocrine studies. However, dynamic studies of the hypothalamic-pituitary axis were performed immediately prior to the second operation and again one month postoperatively. Luteinizing hormone–releasing hormone (LH-RH), 50 μg, and thyrotropin-releasing hormone (TRH), 50 μg, were administered by intravenous bolus. Venous blood samples were obtained at 0, +30, +60, and +90 minutes.

The concentrations of estrone, 17β-estradiol, and progesterone were determined in duplicate by radioimmunoassay. Extraction of samples with ethyl acetate was followed by collection of appropriate fractions by chromatographic separation on LH-20 columns. After this separation and preparation of the internal standards for recovery counts, antisera and tritiated tracer were added. Incubation overnight at 4° C was followed by separation with dextran charcoal. The intra-assay and interassay coefficients of variation for estrone and estradiol were less than 5%. Progesterone coefficients of variation were 4.6% and 12%, respectively.

The serum gonadotropin and prolactin concentrations were determined by double-antibody radioimmunoassay. The standards and antisera were supplied by the National Institutes of Health. All samples were determined in triplicate. In these assays, 0.7 ml of phosphasaline buffer, pH 7.8, with 1% bovine serum albumin was added to 0.1 ml of sample. Antisera, 0.1 ml, was added in concentrations necessary to achieve approximately 30% binding and the samples were incubated at 4° C for 2 days. Iodination of the respective hormones with I^{125} was catalyzed with chloramine-T and the purified tracer was isolated by column chromatography. In all assays the appropriate tracer was added on the third day—0.1 ml adjusted to 5,000 counts per minute (cpm) for the gonadotropins and 10,000 cpm for prolactin (PRL). Two days later the second antiserum was added. After equilibrium was achieved the bound and free fractions were separated and counted. The respective intra-assay and interassay coefficients of variation were 3.6% and 7.5% for luteinizing hormone (LH), 9.5% and 10.7% for follicle-stimulating hormone (FSH), and 7.4% and 11% for PRL. To avoid inter-assay variation, samples from preoperative and postoperative pituitary testing were included in the same appropriate assay. Statistical comparisons were performed with the t test for comparison of paired samples.

Results

Histology. The histologic features of the ovarian tumors were the same on both specimens (Fig. 1). There were large, solid areas of cells and areas of cystic change. The predominant cell type was polygonal with scant, slightly granular, eosinophilic cytoplasm. The nuclei were large and oval and demonstrated diffuse clumping of chromatin. Mitoses were numerous. Clusters of lipid-containing cells were also present. Neither Call-Exner bodies nor crystals of Reinke were identified. The predominant ultrastructural characteristics were those common to steroid-producing cells, e.g., complex swirls of tubular smooth membranes and membrane-bound lipid in the cytoplasm.[2]

Endocrine. The steroid concentrations before and following the initial operation are shown in Table I. By the third postoperative day basal levels for estrone, 17β-estradiol, and progesterone were achieved. Two months following operation steroid concentrations increased. Progesterone increased to 4.3 ng/ml. Estrone and 17β-estradiol increased to 239 and 898 pg/ml, re-

spectively. Following the second operation steroid concentrations again fell to basal levels, and all subsequent values have been normal. The 17β-estradiol concentration has not exceeded 50 pg/ml.

Pituitary function was investigated with LH-RH on two occasions (Fig. 2). Initial testing was performed prior to the second operation when circulating concentrations of gonadal steroids were markedly elevated. LH concentrations increased from 4.3 to 15.5 mIU/ml at +30 minutes, approximately a fourfold rise. The concentration then decreased to basal levels by +90 minutes. FSH concentrations demonstrated little change, rising from 1 to 2 mIU/ml at +30 minutes and returning to basal levels at +90 minutes. LH-RH testing was again performed one month following removal of the remaining ovary, i.e., in a low-steroid environment. Although the basal concentration of LH, 4.6 mIU/ml, was similar to the preoperative basal concentration, the rise to 44.8 mIU/ml at +30 minutes was much greater than the response preoperatively. In a similar fashion, the increase of FSH from 0.8 to 15.4 mIU/ml at +30 minutes was considerably greater than encountered preoperatively. Both responses were significantly different ($p < 0.05$).

The PRL response to TRH was also determined before and after the second operation (Fig. 3). Preoperative and postoperative basal concentrations were 39 and 34 ng/ml, respectively. Although the pattern of response differed slightly, the overall responses were not significantly different ($p > 0.10$).

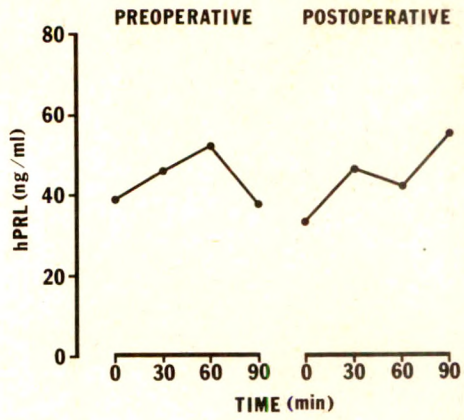


Fig. 3. TRH, 50 μg, was injected intravenously at time 0 on both occasions. The quantitative responses preoperatively and postoperatively were not significantly different although the patterns appear different.

Comment

Ovarian neoplasms in children are generally benign cystic lesions, stromal tumors, or germ cell tumors.[3–5] Approximately 20% to 30% are malignant,[5] and 10% are hormonally active.[6] In the case reported above, marked feminization occurred as a result of steroid secretion by a gonadal stromal tumor. Such tumors are distinctly uncommon in infancy.

Feminizing gonadal stromal tumors generally have been reported as granulosa-theca cell tumors in the past. Reports of these tumors in children are numerous but the number of cases is small. In a recent report from the Ovarian Tumor Registry 307 cases of granulosa-theca cell tumors were presented. Only seven were in children less than 9 years of age.[7] In a review of the literature, records of 52 children under 10 years of age with granulosa-theca cell tumors were collected.[8] Of note, 41 of these 52 children were clinically feminized. Prior to 1941, the youngest child reported with a granulosa-theca cell tumor was 4 years old. Since then several infants with feminizing granulosa-theca cell tumors have been reported.[9–14]

Clinical findings in infants with these tumors are similar to the findings in older children and adults, e.g., abdominal pain, palpable mass, ascites, and feminization. None of these findings, however, are consistently present. Feminization, although common, is not uniformly present,[8, 9] and a mass may be palpable only during anesthesia as in this case. Ascites occurs in 10% to 15% of cases over all and also occurs in children.[4, 15]

Stromal tumors may be less malignant in children, 5% versus 25%,[16] although in one report two of five children died with recurrence.[17] It is difficult in this case to differentiate recurrence from persistence. Since such tumors occur bilaterally in 5% of cases[16, 18] and because the second tumor in this patient developed so rapidly, it would seem likely that the tumor was initially present in both ovaries but not clinically detected.

The luteinization present in this tumor was extensive, resembling closely a luteoma of pregnancy. Luteinization occurs to some degree in 13% of granulosa-theca cell tumors, most commonly in tumors removed during pregnancy.[12] Luteinization, however, may be more common in tumors occuring in childhood. In four children with feminizing tumors all tumors demonstrated marked luteinization.[12] Luteinization was also noted in the tumor of a 9-month-old infant.[13] Whether luteinization is truly more common in children, especially infants, remains to be proved. Regardless, it does seem clear that the presence of luteinized cells is closely associated with steroid secretion.[2]

The abnormal steroid concentrations in this case offer a unique opportunity to examine the HPO axis of infancy. When the preoperative basal gonadotropin concentrations are compared to levels reported for normal infants,[19] LH appears unchanged while FSH is slightly suppressed. This finding suggests increasing

the steroid concentrations above normal does not proportionally increase the negative feedback on tonic LH secretion but does increase the negative feedback on tonic FSH secretion. Two possible explanations for a normal basal LH level in an abnormally high-steroid environment are: (1) LH secretion may be extremely insensitive to negative feedback regulation by gonadal steroids in infancy; (2) normal concentrations of gonadal steroids exert maximal suppression and additional steroids would have no further effect.

Pituitary stimulation with LH-RH was performed preoperatively and postoperatively in an effort to further examine the gonadotropin secretion patterns. The same pattern for stimulated secretion of the gonadotropins was found during preoperative testing, i.e., the LH response was unaffected by the abnormally high steroid concentration while FSH secretion was suppressed. The 3.5-fold rise in LH during preoperative testing with LH-RH, 50 μg, is similar to the threefold rise reported for normal female infants in response to LH-RH, 100 μg.[20] The twofold rise in FSH, however, is less than the eightfold rise reported for the same normal infants. The difference in response is not explainable by the difference in the dosage of LH-RH.[21] A study of nine normal female infants,[22] using a dose of 0.1 mg/M² LH-RH, similar to the dose in this study, confirmed a threefold rise in LH (5.5 to 15.7 mIU/ml). The rise in FSH (6.1 to 24.4 mIU/ml), although somewhat less than previously reported for normal infants, still exceeded the response in this infant preoperatively. Comparison with such published studies, therefore, suggests that high concentrations of steroids further suppress FSH secretion, both basal and stimulated, but have little effect on LH secretion.

These findings, at least in part, are consistent with present concepts of HPO axis development. As recently reviewed,[23] gonadotropin concentrations in fetal serum rise from late in the first trimester to midgestation. Serum levels of both LH (β-subunit) and FSH then decrease progressively to term. The low concentrations at term are associated with high concentrations of gonadal steroids[24] which presumably effect a negative feedback on gonadotropin secretion. Following delivery, steroid concentrations rapidly fall and gonadotropin concentrations later increase, presumably escaping from the negative feedback.[25] The escape of FSH appears to be more pronounced, with concentrations reaching adult levels on occasion. As infancy progresses the gonadotropins again decrease to low concentrations which are maintained until a prepubertal increase.[19, 26–28] These patterns can be explained in part by a gradual increase in hypothalamic-pituitary sensitivity to steroid feedback through fetal life and childhood. The high steroid concentrations in late pregnancy may be necessary to suppress gonadotropin secretion if the hypothalamic-pituitary axis is relatively insensitive at this time. During the neonatal period and infancy, low levels of steroids do not completely suppress gonadotropin secretion, but similar steroid levels become more effective in later childhood. With the onset of puberty a decrease in the sensitivity of the hypothalamic-pituitary axis to the negative feedback of steroids occurs. Gonadotropin and steroid concentrations increase and eventually a positive feedback is acquired.[29, 30]

An increased FSH : LH ratio and a greater FSH response to LH-RH appears characteristic of the infantile HPO axis. This suggests that FSH secretion is less sensitive than LH to the negative feedback of steroids. If normal steroid concentrations effect a maximum negative feedback on LH in infancy, no further decrease in LH secretion would be expected with increased steroid concentrations. Incompletely suppressed FSH secretion, however, would decrease further in response to high concentrations of steroids. This was indeed the finding in this case. The other explanations suggested above for these findings, i.e., the LH secretion is not sensitive to steroid feedback control while FSH secretion is sensitive, seem unlikely. Both LH and FSH secretion increased postoperatively (Fig. 2), providing clear evidence that LH secretion was actively suppressed preoperatively by the gonadal steroids. That steroids exert a negative feedback on both gonadotropins, in children at least, is now accepted.[21, 31]

In contrast to the gonadotropins, basal and stimulated PRL concentrations following TRH, 50 μg, were the same preoperatively and postoperatively. With the exception of the first 6 weeks of life, during which PRL concentrations are increased, the mean PRL concentration for infants is variably reported from 10 to 30 ng/ml.[32, 33] In this case, the basal PRL concentrations preoperatively and postoperatively were both elevated. A stimulatory effect of the gonadal steroids on PRL secretion might explain the preoperative but not the postoperative elevation. Since a progressive decrease in PRL occurs following delivery in both term and premature infants, it appears that infants can metabolize PRL at a rate sufficient to return PRL to normal concentrations within 4 weeks.[32] Thus, the elevated postoperative basal PRL is difficult to explain. Likewise, the similar PRL responses to TRH on both occasions are difficult to interpret. PRL responses in children to both TRH and L-dopa are quantitatively and qualitatively similar to adult responses, but PRL secretion in response to hypoglycemia does not occur in children.[32] It appears that the control of PRL secretion in children is

complex and somewhat different from that in adults, making interpretation of the PRL responses difficult.

The interpretations presented above presume a normal HPO axis acted upon by changing steroid concentrations. The age at onset of the ovarian tumor, its rapid recurrence, and the histologic character of the tumor suggest another, albeit remote, possibility. Hyperstimulation of the ovary by autonomously secreted LH might explain both the ovarian tumor formation and the findings of "normal" LH secretion in an abnormally high-steroid environment. Although there was no evidence of a pituitary tumor in this subject, a functional derangement of the hypothalamic-pituitary axis is possible. The increased LH secretion in response to LH-RH postoperatively, however, demonstrates some functional integrity of the LH control mechanisms. It seems more likely that the abnormalities described simply represent the difference in feedback mechanisms of gonadal steroids on the two gonadotropins, LH and FSH. The differences in control of these two gonadotropins are increasingly apparent and appear to be related to a number of factors, e.g., stage of development, age, sex, and status of gonadal function. This study is an attempt to further define these differences in a unique situation—a feminized infant.

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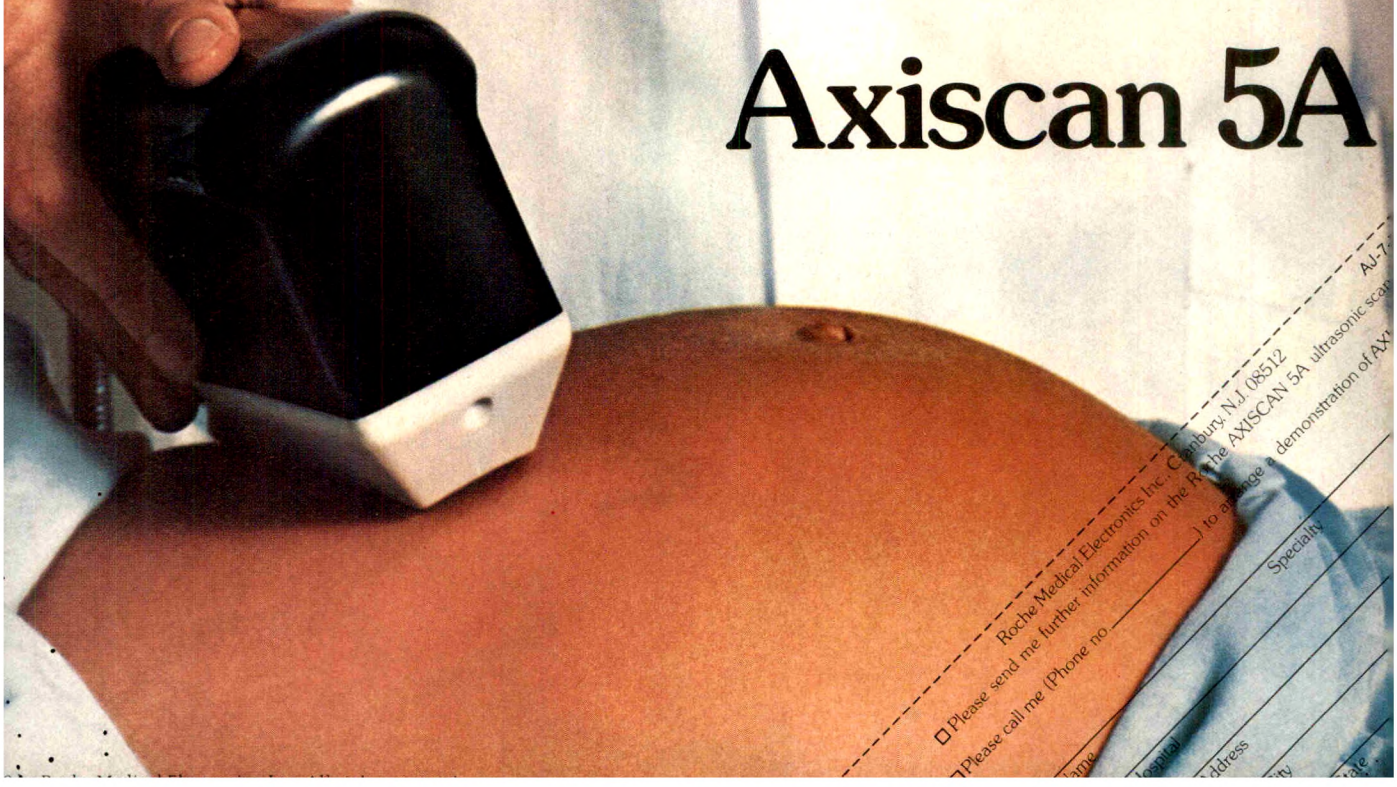
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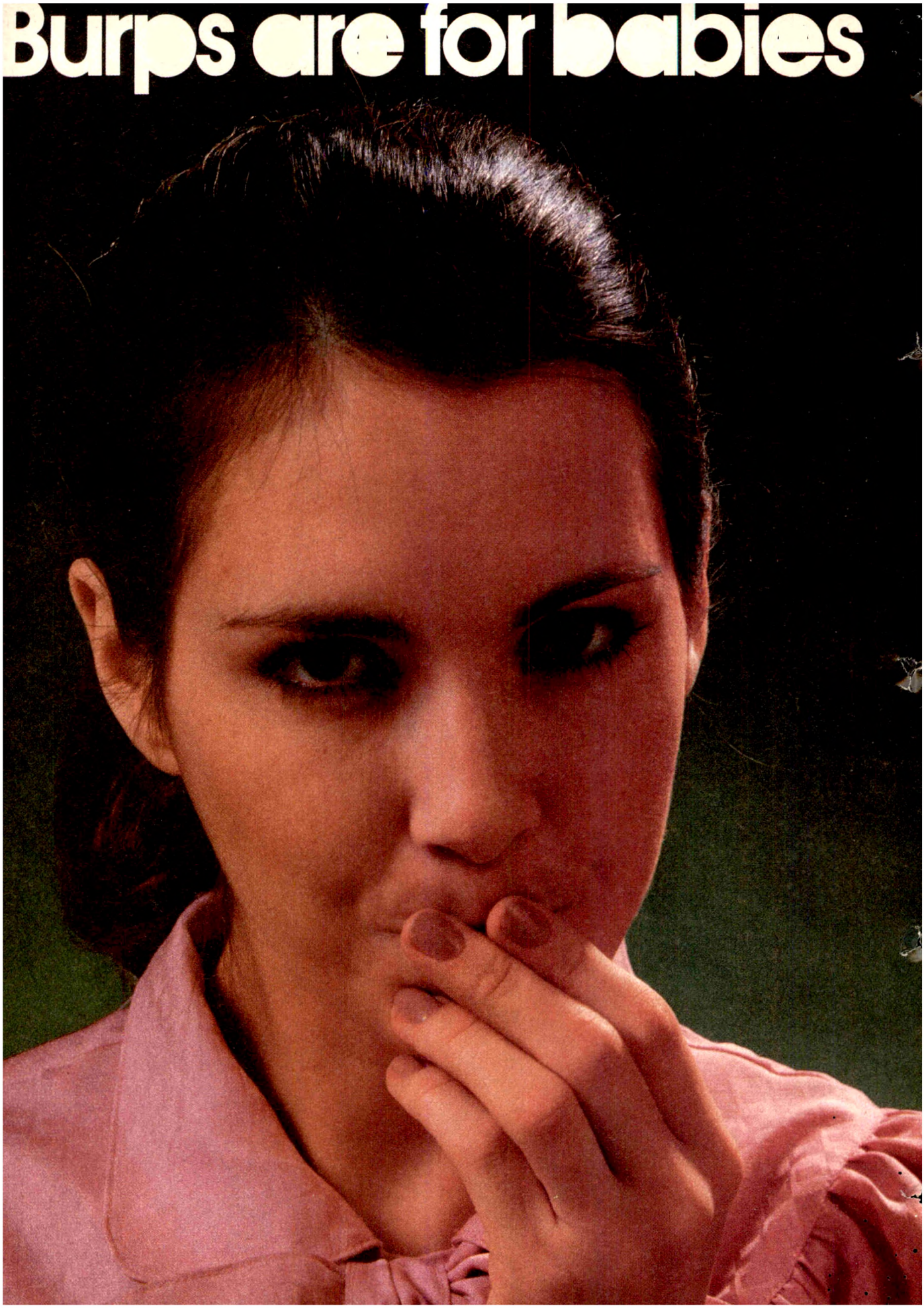
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Usage in pregnancy Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, PERCODAN® and PERCODAN®-Demi should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Usage in children PERCODAN® should not be administered to children. PERCODAN®-Demi, containing half the amount of oxycodone, can be considered.

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Other adverse reactions include euphoria, dysphoria, constipation and pruritus.

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Pregnancy	2.4 (0.42-2.8)	3.1 (0.42-3.8)
Expulsion	18.3 (7.8-29.0)	18.8 (9.0-21.5)
Medical Removal	15.6 (4.8-18.7)	23.2 (9.0-27.0)
Continuation Rate	70.4 (55.2-88.0)	59.8 (57.0-81.5)

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OBSTETRICS

Premature rupture of the membranes: A conservative approach

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A conservative approach was followed in 188 patients with premature rupture of the membranes (PROM) over a 2 year period. There were no neonatal deaths from sepsis, and only one infant showed a positive central bacteriologic culture. Fifty-seven percent of all patients less than 37 weeks' gestation had a latent period of 24 hours and 19% went beyond 7 days before labor began. Patients less than 34 weeks' gestation who received antepartum steroids for lung maturation showed no increased infectious morbidity or mortality. A conservative approach to patients with PROM seems reasonable when either prematurity and/or a cervix unfavorable for induction further complicates the pregnancy. (AM. J. OBSTET. GYNECOL. 134:655, 1979.)

PREMATURE rupture of the membranes (PROM) is a major obstetric complication. It is associated with a high perinatal mortality rate, which is attributed primarily to delivery of premature, low-birth weight infants.[1-6]

The clinical management of patients with PROM is controversial. Infection and prematurity are two major complications. Two main management approaches are being used: (1) aggressive and (2) expectant or conservative.

The aggressive approach consists of delivery within 24 to 48 hours of ruptured membranes.[2, 7-9]

The expectant or conservative approach consists of a "watchful waiting" period with close attention to either spontaneous labor or signs of infection.[4, 6, 10, 11]

Gunn and associates[2] demonstrated an increased perinatal mortality rate after 48 hours of PROM and advocated early delivery. Because of maternal deaths from infection occurring after PROM, Russell and Anderson[12] advocated an aggressive approach.

Recently, Meade and Clapp[8] administered steroids to mothers with PROM in an attempt to accelerate fetal lung maturation[13] in preterm pregnancies. In this study, 27 patients received antepartum steroids and

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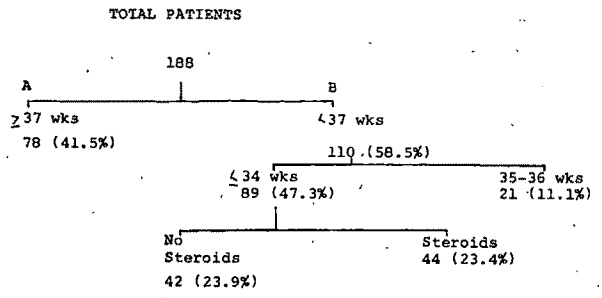


Fig. 1. Distribution of patients with PROM by weeks of gestation at delivery.

were delivered in 24 to 28 hours with a lower rate of respiratory distress syndrome (RDS) and a decreased neonatal mortality rate. They also showed that a conservative approach was not significantly beneficial in prolonging intrauterine development.

On the other hand, Taylor and associates[4] contended that the perinatal mortality rate from PROM is mainly due to prematurity and rarely to infection. He showed a corrected perinatal mortality rate of only 3.5% due to infection in PROM patients. From this he advocated a conservative approach.

In this study we report our results over a two-year period using a conservative approach.

Materials and methods

All patients admitted to St. Margaret's Hospital for Women between July, 1975, and June, 1977, with a diagnosis of PROM and an intrauterine pregnancy greater than 24 weeks were included. St. Margaret's Hospital for Women is a regional perinatal care center in the Greater Boston area receiving high-risk transfers from outlying hospitals. The participants in this study consisted of high-risk referral, clinic, and private patients. Upon arrival at the hospital, a thorough history was taken. Leakage of fluid was documented by a sterile speculum examination. No attempt was made to do a digital examination of the cervix except in cases where patients were thought to be in labor. If no fluid was seen on the speculum examination, fundal pressure was exerted and the patient was asked to perform a Valsalva maneuver to demonstrate any leakage of fluid. Vaginal fluid was tested with Nitrazine paper for pH and swabbed on a slide for ferning or aborization. Vaginal pooling confirmed ruptured membranes, but both a positive Nitrazine test and positive ferning were needed to confirm rupture of the membranes in the absence of pooling. In cases where the history was suggestive of PROM but no confirmation was possible by speculum examination, amniocentesis with instillation of indigo carmine into the amniotic sac was considered. Leakage of the dye into the vagina indicated a slow or minimal leak.

Patients with documentation of PROM were admitted to the hospital and a general physical examination was done. Appropriate laboratory studies were carried out. All patients had fetal heart rate monitoring to observe for signs of occult cord prolapse (variable decelerations) and/or signs of infection (fetal tachycardia).

An ultrasound examination was done on most patients for gestational age and placental localization. In those patients where a clear window of amniotic fluid was found by ultrasound, an amniocentesis was attempted. However, if large amounts of amniotic fluid were lost or if no appropriate window was found, amniocentesis was not carried out. All fluids obtained at amniocentesis were cultured. Lecithin/sphingomyelin (L/S) ratios and optical density 650 measurements[14] were also done. No tocolytic agents or prophylactic antibiotics were used.

If any signs of infection existed, an aggressive approach was instituted, by means of high doses of antibiotics and labor augmentation or induction with intravenous oxytocin. With uninfected patients a conservative approach was begun.

The conservative management consisted of daily complete blood counts, vital signs with temperature every four hours while the patient was awake, daily evaluation of uterine tenderness, and weekly antepartum fetal heart rate evaluations. If signs of infection were not noted, the patients were allowed to go into spontaneous labor. If infection developed, the conservative approach was abandoned, antibiotics were given, and the patients were induced.

All patients less than 37 weeks were managed in the manner described above. However, patients who were 28 to 34 weeks at the time of PROM were also offered antepartum steroids. Betamethasone was given in a dose of 12 mg intramuscularly initially with a repeat dose 24 hours later.

Patients greater than 37 weeks gestation at the time of rupture of membranes were managed somewhat differently. The initial evaluation of these patients was similar to those less than 37 weeks; however, if the speculum examination showed evidence of a favorable cervix for labor induction by the Bishop score,[15] labor was induced. If the cervix was unfavorable, the conservative approach was used. An occasional private patient was induced at this point because the attending physician did not wish to follow a conservative approach.

A pediatrician was in attendance at all deliveries. Most infants were placed in the intensive care nursery for at least 24 hours. The infants were evaluated with a

Table I. Comparison of patients with PROM <37 wk. and ≥37 wk. at delivery

	<37 wk.	*≥37 wk.*	*P value*
No. of patients	110	78	
Range of gestational age (wk.) at ROM	24-36	37-40 (+)	
Latent period:			
>24 hr. <6 days	63 (57%)	12 (15%)	
>7 days	21 (19%)	3 (4%)	
Longest periods (days)	58, 44, 39, 33, 19	14, 12, 9, 7, 3	
Clinical maternal infection at delivery	34 (31%)	10 (13%)	<0.05
Chorioamnionitis by placental examination	32 (29%)	2 (3%)	<0.05
Bacterial colonization:			
Mother (placenta/uterus)	45 (41%)	21 (27%)	<0.05
Infant	33 (30%)	16 (21%)	NS
Antibiotic use:			
Mother	46 (42%)	18 (23%)	<0.05
Infant	70 (64%)	10 (13%)	<0.05
Mode of delivery:			
Vaginal	76 (69%)	50 (64%)	
Cesarean section	34 (31%)	28 (36%)	
Primary	27 (26%)	23 (32%)	
Indications for cesarean section:			
Breech	9	6	
Repeat	7	5	
Lack of progress	7 (6%)	16 (21%)	<0.05
Distress	6 (5%)	1 (1%)	NS
Twins	3		
Transverse lie	1		
Placenta previa	1		

NS = Not significant.

gram stain of the gastric aspirate and by surface, (ear, nose, cord) blood, and cerebral spinal fluid cultures if indicated. Infants felt to be clinically infected were started on antibiotics at delivery. If the cultures were negative and the infant was clinically free of infection, antibiotics were discontinued. Infants who did have clinical or laboratory evidence of infection were treated with antibiotics for at least a 7 to 10 day course. Placentas from these deliveries were cultured for both aerobic and anaerobic bacteria and were sent to the pathology department for study.

Results

In this study, PROM was defined as rupture of the membranes with at least a two-hour latent period before active labor. One hundred eighty-eight patients were admitted to St. Margaret's Hospital with a diagnosis of PROM between July, 1975, and June, 1977. These patients were subdivided by weeks of gestation at the time of delivery into two main groups (Fig. 1): (A) Patients beyond 37 weeks' gestation, and (B) Patients less than 37 weeks' gestation. For purposes of analysis, Group B was further separated into: (1) patients who were 35 to 36 weeks' gestation, and (2) those who were less than or equal to 34 weeks. Patients less than 34 weeks who received steroids for lung maturation were analyzed separately from those who did not.

The patients in Group A (greater than 37 weeks) had shorter latent periods than those with rupture of the membranes less than 37 weeks. In the group with gestational age less than 37 weeks, 63 patients (57%) went more than 24 hours before labor commenced, and 21 patients (19%) went beyond 7 days. The longest latent periods in this group were 58, 44, 39, 33, and 19 days. In the group of patients with gestational ages beyond 37 weeks only 12 (15%) went greater than 24 hours before the onset of labor, and 3 (4%) went beyond 7 days. The longest latent periods in this group were 14, 12, 9, 7, and 3 days.

There was only one positive blood culture in these 188 patients and their offspring. One infant had a Group B beta hemolytic streptococcal septicemia and survived. No infant died of sepsis. Since infectious morbidity as measured by positive central cultures was so low, analysis was made of infectious potential as measured by clinical maternal infection at delivery, chorioamnionitis by placental examination, bacterial colonization, and antibiotic use. These results may be seen in Table I.

The mode of delivery in the two main groups was similar with approximately 65 to 70% of the patients being delivered vaginally and 30 to 35% having cesarean births.

A comparison of the patients less than 34 weeks is

Table II. Comparison of patients with PROM ≤ 34 wk. at delivery with and without steroid use

	Control	*Steroids*	*p Value*
No. of patients	45	44	
Range of gestational age (wk.) at ROM	24-34	26-34	
Latent period:			
>24 hr. <6 days	26 (58%)	28 (63%)	
>7 days	8 (18%)	10 (22%)	
Longest periods (days)	58, 44, 16, 15, 13	39, 33, 19, 17, 13	
Clinical maternal infection at delivery	14 (31%)	21 (48%)	NS
Chorioamnionitis by placental examination	12 (27%)	16 (36%)	NS
Bacterial colonization:			
Mother (placenta/uterus)	14 (31%)	21 (48%)	NS
Infant	9 (20%)	17 (39%)	<0.05
Antibiotic use:			
Mother	18 (40%)	22 (50%)	NS
Infant	22 (49%)	40 (91%)	<0.05
Mode of delivery:			
Vaginal	28 (62%)	35 (80%)	
Cesarean section	17 (38%)	9 (20%)	
Primary	14 (33%)	6 (16%)	
RDS	4 (8%)	6 (14%)	NS

NS = Not significant.

Table III. Comparison of cesarean section rates for lack of progress in patients 37 wk. with induced and spontaneous labors

Labor	*No. of patients*	*No. of cesarean sections*	*Cesarean sections done for L of P**	*% of cesarean sections for L of P**	*P*
Induced	15 (19%)	7 (47%)	7/7	100	<0.05
Spontaneous	63 (81%)	21 (33%)	9/21	43	

*Lack of progress.

seen in Table II. In both the steroid and nonsteroid groups, the latent periods were similar. When the factors used to monitor the potenital for infections were compared there was no statistically significant difference except in bacterial colonizations of the infant and antibiotic use in the infants (p = >0.05).

When the bacterial colonizations were analyzed, the most common organisms isolated in all the groups of patients were similar. The organisms isolated were *Escherichia coli, Staphylococcus epidermidis* coagulase negative, *Enterococci* Group D, and Group B beta hemolytic *streptococci.* Multiple isolations were obtained from some patients.

The incidence of respiratory distress in all of the infants was 6% (11 patients), and all of these occurred in patients less than 37 weeks' gestation. These patients had x-ray and clinical evidence of RDS and needed mechanical ventillation assistance to maintain an adequate Po_2. Since staff opinion varied on the value of antepartum steroids, 45 patients who were 28 to 34 weeks' gestation did not receive antepartum steroids at rupture of the membranes, and 44 patients received steroids in the same gestational age group. There were no deaths due to hyaline membrane disease (HMD) in any infant greater than 28 weeks' gestation at delivery, with or without the use of steroids. There were four patients (8%) who developed RDS in the control group and six patients (14%) who developed RDS in the steroid group (p = N.S.) Table II. The two groups were also compared for Type II RDS which included such diagnoses as wet lung, apnea of the newborn infant, transient tachypnea of the newborn infant, aspiration, etc. There were 15 patients (33%) who developed Type II RDS in the control group and 23 patients (52%) in the steroid-treated group.

A comparison of the cesarean section rates for lack of progress in patients beyond 37 weeks with induced and spontaneous labors was made. Fifteen patients (19%) of the 78 patients beyond 37 weeks at rupture of the membranes were electively induced. The remaining 63 (81%) went into spontaneous labor. Of the patients induced, there were seven patients who had cesarean sections, and all of these were done for lack of progress. Of the patients who went into spontaneous labor, there were 21 patients who had cesarean sections, and of these nine (43%) were done for lack of progress (p = <0.05). These results are summarized in Table III.

There were no maternal deaths in this study. There were, however, 12 perinatal deaths (6.4%), 2 fetal deaths (antepartum stillborns), and 10 neonatal deaths. All of these were in infants weighing less than 1,000

Table IV. Mortality rate in PROM group

Case No.	*Gestational age at ROM*	*Gestational age at delivery*	*Celestone use*	*Birth weight (GM.)*	*Duration of ROM*	*Apgar*	*Age at death*	*Delivery route*	*Presentation*	*Autopsy*
1	24	24	–	630	24 hr.	0/0	Stillborn	Vaginal	Breech	Previable, multiple congenital anomalies, 45, XY, 13/14 translocation
2	24	24	–	480	13 days	0/0	Stillborn	Vaginal	Breech	Prolapsed cord on admission, previable, intrauterine anoxia, severe acute chorioamnionitis and funisitis
3	28	28	16 hr.	936	48 hr.	1/5	5 days	Vaginal	Breech	Intra-alveolar edema and hemorrhage with no expansion, HMD, residual
4	24	24	–	624	2 days	3/3	1 hr.	Vaginal	Vertex	Marked immaturity
5	25	26	–	850	6 days	5/6	5 hr.	C/section	Vertex	Immaturity, respiratory failure, HMD
6	26	26	–	936	13 hr.	2/3	3 hr.	Vaginal	Vertex	Previable, neonatal anoxia, severe chorioamnionitis
7	25	25	–	680	24 hr.	7/7	40 hr.	Vaginal	Breech	Previable, bilateral acute bronchopneumonia
8	28	28	–	1,191	14 hr.	1/1	1½ hr.	C/section	Breech	"Incomplete Potter" syndrome, hypoplastic lung, normal genitourinary system
9	30	30	–	964	12 hr.	0/1	15 hr.	C/section	Vertex	Epidermolysis bullosa, hypoplastic lung, pyloric atresia
10	24	24	–	790	34 hr.	0/2	2 hr.	Vaginal	Vertex	
11	24	24	–	539	2½ days	4/4	1 hr.	Vaginal	Vertex	
12	40	40	–	3,629	12 hr.	1/0	½ hr.	Vaginal	Vertex	Pulmonary hypoplasia with hypoplasia of right diaphragm, spina bifida meningomyelocele, normal genitourinary system

HMD = Hyaline membrane disease.

grams except for two infants weighing more than 1,000 grams with congenital anomalies. There were a total of four patients who had congenital anomalies incompatible with sustained life (Cases 1, 8, 9, and 12). There were no neonatal deaths attributable to neonatal sepsis in an infant who by birth weight and gestational age was considered viable (greater than 1,000 grams or greater than 28 weeks' gestation). Every infant that was considered viable survived, if no congenital anomalies existed leading to the infant's death. Examinations of the deaths by gestational age and birth weight at delivery were carried out (Table IV). All infants with a birth weight less than 700 grams and less than 24 weeks' gestation died. Those infants between 800 and 1,000 grams had a 50% mortality rate (3/6). Likewise, the infants between 25 and 28 weeks' gestation showed less than a 50% mortality rate (4/12). Infants with congenital anomalies incompatible with sustained life were excluded from these analyses.

Comment

The greatest fear or contraindication to a conservative approach in patients with ruptured membranes is the risk of infection. In this study no babies died from infection, either sepsis or neonatal pneumonia, and only one patient (infant) had a positive blood culture. Perhaps our avoidance of bimanual examinations minimized the risk of ascending infection in our population. There was no significant maternal morbidity and no maternal deaths despite a higher potential for infection at delivery as indicated by such parameters as clinical infection at the time of delivery, chorioamnionitis on placental examination, and bacterial colonization. It would appear that the conventional parameters

of temperature, uterine tenderness, and white blood cell count generally used to assess maternal clinical infection at delivery are not suitable indicators for actual infectious morbidity. In fact approximately 50% of those thought to be infected at delivery did not show infection by placental examination for chorioamnionitis or bacterial colonization. Similarly, approximately 50% of those not thought to be infected did show chorioamnionitis or had positive bacterial colonizations. The work of Townsend and colleagues[6] would support this belief. The parameters of pathologic examination of the placenta and bacterial colonization can also be erroneous, since they can be influenced by factors such as length of rupture of the membranes and route of delivery, without indicating true infection.

Since prematurity is accompanied by complications such as RDS, necrotizing enterocolitis, intracranial hemorrhage, and aspiration, any prolongation of intrauterine existence would be expected to reduce the risk of death. One hundred ten patients in this study were less than 37 weeks at the time of rupture of the membranes and were therefore at risk for these complications. Approximately 60% had a latent period greater than 24 hours and almost 20% had a latent period greater than 7 days. The longest latent period was 58 days. A continued in utero existence of these infants would appear to be the major contributing factor responsible for their successful outcome.

Eighty-nine patients in this study were less than 34 weeks and were as a result, candidates for antepartum steroid therapy to accelerate fetal lung maturation.[13] A decreased incidence of RDS could not be demonstrated, however, in the infants of the steroid-treated mothers, probably because of the small number of infants in this study who actually developed RDS. Interestingly, neither was there an increased potential for infection in steroid-treated mothers or their infants (Table II). The only parameters that were significantly different in the steroid versus nonsteroid patients were infant bacterial colonizations and infant antibiotic use. The first may be explained by the significantly increased rate of vaginal deliveries in the steroid-treated group with resultant bacterial contamination of the infant on its passage through the vagina. The increased use of antibiotics is explainable by the aggressiveness of the pediatric service to use prophylactic antibiotics.

The availability of an intensive care nursery certainly contributed to the low morbidity and mortality rates observed in this study. From our results it would appear that all patients with PROM who are less than 37 weeks' gestation should be referred to a perinatal center where an intensive care nursery awaits the premature infant.

Seventy-eight patients in this study were beyond 37 weeks and the majority of these were managed conservatively. Interestingly, 100% of the cesarean sections on induced patients in this group were done for lack of progress in labor. This compares to a 43% cesarean section rate for lack of progress in patients who had spontaneous labor (Table III). In the electively induced patients who had cesarean sections, it was also observed that some of the patients had delivered larger babies vaginally in previous pregnancies. Because infection was a minor problem in this study, the indiscriminate use of labor inductions in patients with PROM at term seems unwarranted. Only 12 patients (15%) of those beyond 37 weeks gestation at the time of rupture of the membranes went more than 24 hours before labor commenced, and only three patients (4%) went beyond one week. This suggests that careful observation of these patients within the hospital is reasonable and practical, and that such a scheme may decrease the morbidity and mortality rate from an increased cesarean section rate.

Summary

From this study we may conclude the following: (1) The conservative approach in the management of patients with PROM is safe and beneficial. Morbidity and mortality rates in both mother and infant are low as in utero development continues. (2) The use of steroids to accelerate fetal lung maturation does not seem to increase the risk of infection. (3) A conservative approach in a term pregnancy with PROM and an uninducible cervix seems to decrease the incidence of cesarean sections without an appropriate increase in the infectious morbidity. (4) Patients with premature ruptured membranes prior to 37 weeks should be treated at a perinatal care center where an intensive care nursery is available. (5) The lack of digital examinations in this study may account for the low incidence of infectious morbidity.

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Thalassemia and pregnancy: Results of an antenatal screening program

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A thalassemia screening program was implemented at our institution using the finding of a mean corpuscular volume < 80 fl as the index of abnormality. Further evaluation using hemoglobin (Hb) electrophoresis and serum iron studies was carried out according to the scheme detailed below. A diagnosis of thalassemia was made in 33 women (42 pregnancies). Eight patients had α-thalassemia trait, 23 β-thalassemia trait, and two Hb H disease. Thalassemia trait did not have any adverse effect on pregnancy outcome. In two couples the fetuses were at risk for homozygous disease and in one couple the fetus was at risk for sickle cell β-thalassemia. The screening program described is an effective and inexpensive means of detecting thalassemia in an antenatal population and is applicable to most every clinic or office setting. (AM. J. OBSTET. GYNECOL. 134:662, 1979.)

THE THALASSEMIAS are a genetically determined, heterogenous group of disorders characterized by reduced production of one or more of the globin chains in human hemoglobin. Consequently, hemoglobin synthesis is impaired. Moreover, the partner chains which are produced at a normal rate, but in relative excess, accumulate. Precipitation of these excess unpaired globin chains results in ineffective erythropoesis, red cell sequestration and destruction, and hypochromic anemia.[1] The most severe forms of this disorder may cause intrauterine or childhood death. A person who is heterozygous, or a carrier, for a thalassemia trait may be asymptomatic and, therefore, unaware of his/her condition until a mating with another carrier produces a severely affected child.

During the past decade substantial progress has been made in our understanding of the molecular defects in thalassemia; however, there is still no cure for the disease. At present we must rely on prevention: either preventing the conception of an affected fetus or, once conceived, preventing its birth. The first alternative would require a degree of social engineering unacceptable to most people. Fortunately, remarkable advances in the field of prenatal diagnosis now make it possible to detect a thalassemic fetus in utero and, hence, in combination with selective abortion, to avoid the birth of a child doomed to illhealth and an early death.

This paper will discuss: (1) the molecular basis and pathophysiology of thalassemia, (2) the methods for screening and detection in adults, in particular during pregnancy, and (3) the methods of prenatal diagnosis. We will conclude by presenting a suggested protocol for antenatal screening of thalassemia and the results of implementing this program at our institution during the years 1975 to 1978. These results lead us to recommend widespread antenatal screening.

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Background

Hemoglobin is a tetrameric protein consisting of four globin chains. In humans there are six structurally different types of globin chains, designated α, β, γ, δ, ϵ, and ζ.[2] Most pertinent to the thalassemias are the α-, β-, γ-, and δ-chains. The early embryonic globins ϵ and ζ are rapidly replaced as the fetus develops.[3] Two α-chains and two non-α-chains combine to form each of the different hemoglobins found in adults. Normally Hb A ($\alpha_2\beta_2$) constitutes 96% of adult hemoglobin while Hb A_2 ($\alpha_2\delta_2$) contributes an additional 2 to 3%. The predominant hemoglobin during fetal life, Hb F ($\alpha_2\gamma_2$)

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comprises less than 2% in the adult, except when certain conditions, including pregnancy, supervene.[4]

The messenger ribonucleic acid (RNA) for each globin chain is transcribed from a varying number of genes which may differ among populations. It appears that there are four genes controlling α-chain synthesis in Oriental and Caucasian people[5] but an inconstant number, from two to four, in black populations.[6] There are two genes each for β- and δ-chains and at least four for γ-chains.[7] The β-, δ-, and γ-genes are closely linked on the same chromosome, while the α-genes are thought to reside on another chromosome.[8]

The thalassemia syndromes are named and classified by the type of chain which is inadequately represented. The two major groups are the α- and β-thalassemias, both of which affect the synthesis of Hb A. Reduced synthesis of γ- and δ-chains, and even combinations in which two or more globin chains are affected (e.g., δβ-, γβ-, hereditary persistence of fetal hemoglobin [HPFH]) have been reported, but these are rarer.[9–11] In each instance the thalassemia is a quantitative disorder of globin synthesis; structurally the chains are entirely normal. There is no single etiology of the disease. On the molecular level, a variety of defects have been demonstrated, each involving a different step along the pathway of transcription of gene deoxyribonucleic acid (DNA) into messenger RNA (m-RNA) and translation of m-RNA into globin chains.

In the most common form of α-thalassemia one or more structural genes are physically absent, permanently deleted from the genome.[12] In the homozygous condition, when all four genes are deleted, no α-chains are produced and the fetus is unable to synthesize Hb F or any of the adult hemoglobins.[13] The predominant hemoglobin is Hb Barts (γ_4) which releases inadequate amounts of oxygen to tissues because of its high oxygen affinity. The result is high-output heart failure, hydrops fetalis, and a stillborn fetus.

The most severe form of α-thalassemia compatible with extrauterine life is Hb H disease which results from the deletion of three genes.[14] In patients with this disease abnormal quantities of both Hb H (β_4) and Hb Barts accumulate. β_4-Tetramers precipitate during the life of the red cell to form inclusion bodies. The "pitting out" of these bodies by the reticuloendothelial system causes moderately severe hemolytic anemia. In α-thalassemia minor (α-thalassemia-1) two genes are deleted, causing a mild hypochromic, microcytic anemia which must be differentiated from iron deficiency.[6] A single gene deletion (α-thalassemia-2) is clinically undetectable or the "silent carrier" state.

α-Thalassemia may also result from a nondeletion defect.[15] All genes are present, yet the phenotype is that of α-thalassemia 1. Apparently only a small amount of globin can be synthesized from these genes. Still another group of defects is exemplified by mutant hemoglobins such as Hb Constant Spring where an elongated α gene product is incorporated into the Hb molecule.[16] A greatly reduced amount of this mutant product is produced.

The etiology of α-thalassemia in black people is less clear than for those who are Oriental and Caucasian. They do not demonstrate an imbalance as marked or consistent in globin synthesis. Hgb H disease is seen very rarely and thalassemia minor is clinically very mild, apparently because the α-thalassemia in this population involves both deletion and nondeletion mutations or a variable number of genes influencing m-RNA concentration in reticulocytes.

Unlike α-thalassemia, a gene deletion has not been demonstrated in β-thalassemia. There are two forms of β-thalassemia, designated β^+ and β^0, depending on whether β-chain production is reduced or entirely absent. In β^+ thalassemia, m-RNA for β-globin chains is present but is quantitatively reduced.[17] This might be due to a particularly unstable m-RNA or to a decreased rate of transcription of m-RNA.

In some cases of β^0-thalassemia m-RNA is present, but there is defect in its translation which might be explained by an abnormal m-RNA.[18] In the Ferrara type of β^0-thalassemia the translation may be corrected in vitro by the addition of ribosome-free supernates from normal reticulocyte lysates,[19] and it has been postulated that a necessary translation control factor, perhaps acting at globin chain initiation, is missing while the m-RNA itself is normal.[20] In other cases the β-globin gene is present but no detectable m-RNA is found in the reticulocyte.[21, 22] Possible explanations include a mutation in the initiation region for transcription, preventing the synthesis of m-RNA, rapid breakdown of transcribed m-RNA before it can be translated, or failure of m-RNA to be processed from the nucleus to the cytoplasm.[22] Reduced β-chain synthesis may also be seen with Hb Lepore, a product of δ-and β-gene crossover, HPFH, and in δβ-thalassemia. HPFH and δβ-thalassemia differ from β-thalassemia in that they both involve β-gene deletions.[23]

In the homozygous β-thalassemia condition, α-chain production is unimpeded and these highly unstable chains accumulate and eventually precipitate. Markedly ineffective erythropoiesis and severe hemolysis result in a condition known as thalassemia major or Cooley's anemia.[24] The affected infant is anemic by 3 months of age, has hepatomegaly, requires blood transfusions every 3 to 4 weeks, and dies by the third decade, usually of myocardial hemosiderosis. Those

female patients surviving until puberty are usually amenorrheic with severely impaired fertility.[25] In the heterozygous state (thalassemia minor) the normal β-globin gene allows developing red cells to accumulate up to 75% of the normal complement of Hb A.[6] The remaining deficit is partially corrected by production of an increased number of smaller than normal cells. This results in the hypochromic microcytosis of β-thalassemia trait, but the individual may not be clinically anemic. Because δ-chain synthesis is increased relative to β-chain synthesis, the Hb A_2 level is also increased.

The clinical severity of β-thalassemia is influenced by the extent to which γ-chain production can compensate for deficient β-chain synthesis. Approximately 50% of patients with β-thalassemia trait have elevated Hb F levels, and in δβ-thalassemia there is a marked increase in Hb F, which acts to ameliorate this condition. The rare instances of pregnancy in patients reported to have thalassemia major most likely occurred in individuals actually heterozygous for two different β-thalassemia genes, at least one of which is a "high F" form.[25, 26]

Due to the marked heterogeneity of the thalassemia syndromes there is no single diagnostic method applicable to all cases. Except for genetically obligate heterozygous persons, the β/α globin synthetic ratio provides the most accurate method of identifying thalassemia trait.[27] It is the only means of detecting α-thalassemia-2. However, it is generally unavailable and too elaborate for routine clinical use. (It also may not detect cases of combined α-and β-thalassemia.) Currently, an elevated Hb A_2 level (>3.5) is considered sufficient evidence to substantiate a diagnosis of β-thalassemia trait. Hb A_2 levels are normal in α-thalassemia and, hence, this is a diagnosis of exclusion made only after iron deficiency has been ruled out. In δβ-thalassemia, Hb A_2 levels will also be normal but Hb F levels will be increased.[2] Red blood cell morphology and osmotic fragility measurements provide additional evidence of the thalassemic state.

Thalassemia is found throughout the world but is concentrated in the Mediterranean coastal areas, central Africa, and parts of Asia. In these regions it is believed that the high incidence represents a balanced polymorphism due to heterozygous advantage.[1] Persons who are heterozygous are protected against malaria when compared to the homozygous normal.

All forms of thalassemia are inherited as an autosomal recessive trait. The lethal homozygous state results only when all of an individual's genes for the α- or β-chain are affected. If a couple, each of whom is heterozygous for the same condition (carriers), chooses to have children they have a 25% chance of conceiving an affected fetus and a 50% chance that the fetus will be heterozygous.

Antenatal diagnosis

Until very recently, the obstetrician has had little to offer patients who were α- or β-thalassemia carriers. They usually had uncomplicated pregnancies and the obstetrician's role was limited to genetic counseling and performing abortions for those couples fearful of delivering an affected child. The development of methods to diagnose thalassemia in utero now allows the obstetrician to give parents definite answers rather than statistical probabilities. Couples at risk can avoid having affected children without remaining childless and are spared months of anxiety awaiting the outcome of a pregnancy.

Since the homozygous state is invariably fatal, α-thalassemia does not produce the major medical and social problems associated with β-thalassemia. Even so, early diagnosis is desirable to minimize the emotional trauma of an unsuccessful pregnancy and to prevent the development of third trimester pre-eclampsia which frequently accompanies this disease.[28]

The method for prenatal diagnosis of α-thalassemia involves measuring the number of intact α-globin structural genes present in the cellular genome using the technique of molecular hybridization.[29] Since any nucleated cell, including amniotic fluid fibroblasts, contains the full complement of globin genes, amniocentesis provides fetal cells which can be cultured and then analyzed. Using reverse transcriptase, a viral enzyme which transcribes DNA from RNA, complementary α-DNA (c-DNA) can be transcribed from α-globin m-RNA. This complementary DNA is also complementary to and capable of binding to α-globin structural genes in cells. The rapidity with which the c-DNA binds to DNA from amniotic fibroblasts is proportional to the number of copies of α-globin structural genes present in the cells. This technique clearly distinguishes the homozygous state from carrier or normal states.

Since the known molecular defects in the β-thalassemias do not involve gene deletions, antenatal diagnosis depends upon actually quantitating the fetal production of Hb A. A number of investigators have demonstrated the presence of Hb A during the first trimester, with β-chain synthesis increasing as the pregnancy progresses.[30, 31] By measuring the synthesis of globin chains, the normal ratio of β- to γ-chain synthesis has been determined for varying gestational ages.[32, 33] By comparing the β/γ synthetic ratio of a sampled fetus to that of normal fetuses of the same

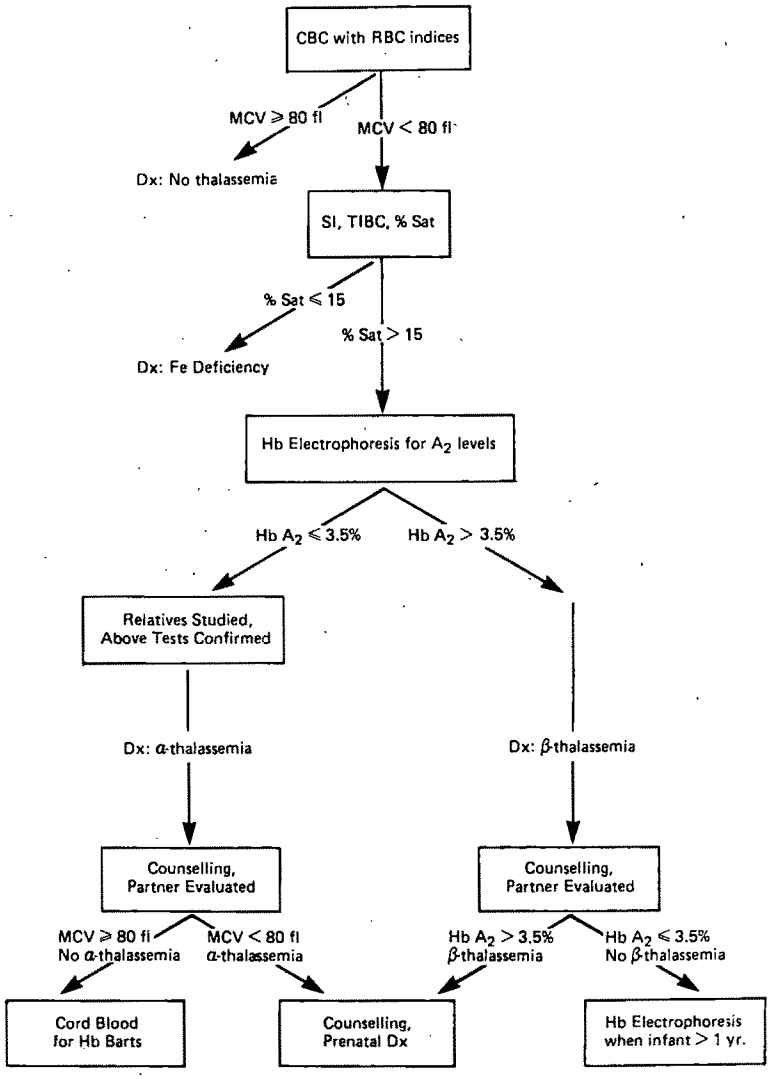


Fig. 1. Scheme for antenatal thalassemia program.

gestational age, the presence of β-thalassemia can be detected. However, such synthetic studies require fetal erythrocytes.

Fetal blood may be aspirated under direct visualization using a modified cannula through which both a fetoscope and a 26 gauge blood drawing needle can be inserted transabdominally.[34] The rigid fetoscope renders this technique unsuitable for some anterior placentas. Using fetoscopy, it has been possible to obtain sufficient fetal red blood cells for hemoglobin synthesis studies from approximately 90% of patients.[35] A second technique for obtaining fetal blood is by sonographically directed placental aspiration through a 20 gauge needle.[36] In our hands this technique has been successful in obtaining samples from 86.4% of anterior placentas and from 94.4% of posterior placentas. Over 40 pregnancies have been evaluated.[35] Regardless of technique, sampling should be performed at approximately 18 to 20 weeks gestation. As pregnancy progresses any given amount of blood loss represents a smaller proportion of the total fetal blood volume and yet this is sufficiently early to terminate a pregnancy, if required. At 18 to 20 weeks' gestation the normal β/γ ratio is >0.07 with a mean of 0.11, the ratio for the heterozygous state is 0.058 ± 0.020 ($\pm$2SD) and the ratio for the homozygous state in all reported cases has been <0.03.[37]

Both blood sampling procedures result in a mixture of fetal and maternal blood. Since fetal erythrocytes synthesize globin chains at rates greater than 500 times that of maternal cells, the maternal contribution to the sample's β-chain synthesis is small.[38] If the sample con-

Table I. Hematologic diagnoses

Diagnosis	*No. of patients*	*No. of pregnancies*
α-Thalassemia trait	8	9
β-Thalassemia trait	23	31
Hg H disease	2	2
Total	33	42

tains less than 50% fetal cells, these can be separated from the mixture by agglutination with anti-i, an antibody which binds only to fetal cells.[39] This method has been successful in analyzing samples containing as little as 7% fetal red cells and eliminates the need to suppress maternal erythropoiesis by transfusions.

Antenatal diagnosis of β-thalassemia is not without hazard. The risk of fetal loss is approximately 10%.[40, 41] The two reports of inaccurate diagnoses were early in one center's experience and with the additional expertise now gained are unlikely to recur.

Antenatal screening

The availability of prenatal diagnosis provides strong impetus for the creation of mass maternal screening programs. Since the primary aim of screening is the detection of individuals who already carry the gene and the prevention of homozygous individuals in the future, the ideal population for evaluation is women of reproductive age. A good screening method should have no false negative and few false positive results. It should be inexpensive, simple to perform, and acceptable to patients. Protocols which center upon the determination of red blood cell indices are particularly appealing, since they presently afford the greatest potential for meeting the above criteria.

Several proposals may be found in the literature. Healy suggests that all individuals in whom the function (0.23 × mean corpuscular volume[MCV]) − (0.22 × red blood cells) − (0.93 × Hg) − 3 is less than zero have thalassemia.[42] England and Fraser[42] simplified the formula to MCV − red blood cells − 5 × Hg − 3.4 < 0. Mentzer[43] advocates using the ratio of MCV/red blood cells, values less than 13 corresponding to patients with thalassemia. Recently, Shine and Lal[44] have developed a heuristic method which they claim yields the lowest false negative rate and an acceptable number of false positive results: $MCV^2 \times$ mean corpuscular hemoglobin (MCH) < 1,530.

At our institution we have implemented a thalassemia screening program specifically designed to evaluate obstetric patients. We believe this protocol provides the information most pertinent to the pregnant patient while retaining the virtues of simplicity and low cost. Each patient registering for prenatal care at our clinic has a complete blood count with red blood cell indices performed at the time of the first prenatal visit. This includes measurement of the MCV by a Coulter electronic counter. If the MCV is less than 80 fl (similar to Pearson's[45] threshold of 79 fl), the patient is further evaluated following the scheme outlined in Fig. 1. In addition to thalassemia, microcytic, hypochromic anemia may be due to iron deficiency, chronic illness, or sideroblastic anemia. To differentiate between these disorders serum iron studies are performed (serum iron, iron binding capacity, percent saturation). If iron studies are normal (serum iron greater than 50 μg/dl, saturation greater than 15%) the Hb A_2 level is determined. A level greater than 3.5 is considered diagnostic of β-thalassemia trait. If the Hb A_2 is less than 3.5 all studies are repeated and the patient's relatives are evaluated if possible. A diagnosis of α-thalassemia is made only when microcytosis, normal serum iron studies, and a normal level of Hb A_2 are confirmed. A diagnosis of Hb H disease is made if, in addition, hemoglobin electrophoresis demonstrates β_4.

Serum iron studies were chosen as the second diagnostic step for several reasons. By far the largest number of false positive results using Pearson's threshold will be due to iron deficiency. Indeed, pregnant patients, including those with thalassemia trait, are at particular risk for this condition. However, patients with thalassemia are often misdiagnosed and treated with iron for years without response. This may lead to iron overloading, particularly if parenteral iron is used.[46] Since it is desirable to treat all iron-deficient patients but inappropriate to do so without first verifying the diagnosis, determination of iron status would properly follow even if the obstetrician were uninterested in thalassemia. By eliminating microcytosis secondary to iron deficiency fewer hemoglobin electrophoreses are required. Finally, in cases of coexistant β-thalassemia and iron deficiency, Hb A_2 levels may be depressed below 3.5 and the diagnosis missed. In this event A_2 levels may become elevated only after iron replacement.[46] If after appropriate iron therapy microcytosis persists, a repeat Hb A_2 level is performed.

Once a diagnosis of thalassemia has been made the patient is informed as to its possible significance and her partner is evaluated by means of a complete blood count and hemoglobin electrophoresis. If he is found to be a carrier of a like thalassemia trait, or is heterozygous for a hemoglobinopathy that in the double heterozygous state with thalassemia trait causes clinical disability, the couple receives genetic counseling and is offered prenatal diagnosis as described above.

Antenatal thalassemia screening was begun at our institution in the fall of 1975. We have examined the

Table II. Hematologic parameters in thalassemic patients during the first trimester of pregnancy

Hematologic parameter	*All thalassemias*	*α-Thalassemia*	*β-Thalassemia*
Hemoglobin (gm/dl)	10.66 ± 0.98*	10.92 ± 0.77	10.61 ± 1.03
	N = 28†	N = 9	N = 19
Hematocrit (%)	33.48 ± 2.76	33.67 ± 2.32	33.41 ± 3.13
	N = 26	N = 9	
N = 17			
RBC (× 10^9/1)	4.91 ± 0.58	4.90 ± 0.57	4.94 ± 0.63
	N = 24	N = 9	
N = 15			
MCV (fl)	68.54 ± 5.30	68.80 ± 4.02	68.20 ± 6.26
	N = 24	N = 9	N = 15
MCH (pg/red blood cell)	22.17 ± 2.95	23.09 ± 3.95	21.73 ± 2.07
	N = 24	N = 9	N = 15
MCHC (gm/dl red blood cells)	31.95 ± 1.21	32.35 ± 0.93	31.97 ± 0.84
	N = 25	N = 9	N = 16
Hb A_2 (% total hemoglobin)	4.85 ± 1.61‡	2.83 ± 1.10‡	5.72 ± 1.10‡
	N = 10	N = 4	N = 6
Hb F (% of patients with Hb F >2%)	40.0	20.0	60.0
	N = 10	N = 5	N = 5

*± Standard deviation.
†N = Number of pregnancies.
‡p = 0.003 using two-tailed t test.

results of this program along with our previous data on thalassemic patients in order to assess: (1) conflicting reports on the effect of thalassemia on pregnancy and vice versa, and (2) the impact of the thalassemia screening program.

Subjects and methods

Between July, 1970, and February, 1978, approximately 10,000 pregnancies were observed at our prenatal clinic. Using the criteria described above, a diagnosis of thalassemia was noted in 42 pregnancies in 33 women. Patients were ascertained by several means. In some cases the diagnosis was discovered in the course of evaluating a persistent anemia of pregnancy. In others, the diagnosis was known prior to presentation at the clinic and one patient was specifically referred for prenatal (fetal) diagnosis. Subsequent to implementing the screening program the majority of patients were detected by screening. Several patients discovered by our screening program were found to have had previous pregnancies during which the diagnosis had remained unrecognized. For the purposes of analysis these earlier pregnancies were examined in retrospect.

All patients received routine obstetric care without consideration of the diagnosis. Data concerning the maternal hematologic status, prior obstetric history, and obstetric and fetal outcome were abstracted, key punched, and analyzed by an IBM 370 computer. Statistical analyses using chi-square and Student's t tests were performed with the Statistical Package for the Social Sciences (SPSS). The total obstetric population registered at our clinic between January, 1976, and March, 1978, (4,574 pregnancies) served as control subjects. Only p values < 0.05 were considered significant.

Table III. Comparison of mean hemoglobin and hematocrit values in each trimester by diagnosis

Hematologic parameters	*α-Thalassemia*	*β-Thalassemia*
Hemoglobin (gm/dl):		
First trimester	10.9 ± 0.77*	10.6 ± 1.03
	N ± 9†	N = 19
Second trimester	11.1 ± 0.62‡	10.0 ± 0.83‡
	N = 5	N = 23
Third trimester	10.9 ± 0.78	10.4 ± 0.92
	N = 9	N =26
Hematocrit (%):		
First trimester	33.7 ± 2.32	33.4 ± 3.13
	N =10	N = 17
Second trimester	34.7 ± 1.45§	31.6 ± 2.02§
	N =5	N = 22
Third trimester	33.9 ± 1.81	32.8 ± 2.38
	N =9	N = 25

*± Standard deviation.
†N = number of pregnancies.
‡p = 0.014.
§p = 0.005.

In the fall of 1975, thalassemia screening was implemented as described above. Complete blood counts and red blood cell indices were performed using a Coulter counter model S.* Serum iron studies were determined by the Auto-Clinical Analyzer† using bath-

*Coulter Electronics, Hialeah, Florida.
†Technicon Corp., Tarrytown, New York.

Table IV. Various characteristics of mothers and fetuses

Maternal/fetal observations	*Control*	*All thalassemias*	*α-Thalassemia*	*β-Thalassemia*
Gestational age at delivery (wk.)	39.53 ± 2.8*	39.1 ± 2.8	39.6 ± 2.2	39.0 ± 3.0
	N = 4,506†	N = 38	N = 9	N = 29
Method of delivery (%):				
Spontaneous	55.1	61.5	77.8	55.2
	N = 2,486	N = 24	N = 7	N = 16
Forceps or vacuum	23.0	23.1	11.1	27.6
	N = 1,037	N = 9	N = 1	N = 8
Cesarean section	21.9	15.4	11.1	17.2
	N = 986	N = 6	N = 1	N = 5
Birth weight (gm)	3,312 ± 663	3,117 ± 638	3,298 ± 403	3,077 ± 693
	N = 4,336	N = 38	N = 9	N = 29
Placental weight (gm)	658 ± 163	540 ± 157	592 ± 178	519 ± 148
	N = 4,061	N = 23	N = 8	N = 15
Ratio fetal weight to placental weight	5.18 ± 1.42	6.09 ± 2.19	6.40 ± 3.18	5.88 ± 1.64
	N = 3,896	N = 23	N = 8	N = 15
Fetal maturity-weight (%)				
Small for gestational age	5.1	5.3	0	6.9
	N = 201	N = 2	N = 0	N = 2
Appropriate for gestational age	83.7	89.5	88.9	89.7
	N = 3,280	N = 34	N = 8	N = 26
Large for gestational age	11.2	5.3	11.1	3.4
	N = 440	N = 2	N = 1	N = 1
Premature (%) (≤37 wk.)	13.7	15.8	11.1	17.2
	N = 536	N = 6	N = 1	N = 5
Mature (%) (38-42 wk.)	58.1	89.6	88.9	79.3
	N = 2,277	N = 31	N = 8	N = 23
Postmature (%) (>42 wk.)	28.3	2.6	0	3.4
	N = 1,109	N = 1	N = 0	N = 1

*± Standard deviation.
†N = Number of pregnancies.

ophenanthroline sulfonate. Hemoglobin electrophoreses were determined using a cellulose acetate membrane and quantitated by densitometer. Hg A_2 levels were run against both normal and abnormal controls. After obtaining informed consent, antenatal diagnosis was performed as described by Kan and associates.[30, 47] Neonatal cord blood specimens were analyzed for Hb Barts and quantitated by densitometer.

Results and comment

The maternal diagnoses in 42 pregnancies were distributed as shown in Table I. Four patients had additional hematologic diagnoses possibly influencing their results. One patient with α-thalassemia had sickle trait. Among β-thalassemic patients there were single incidences of iron deficiency, aplastic anemia, and the carrier state for combined immune deficiency disease.

Hematologic variables. First-trimester hematologic parameters for each type of thalassemia are displayed in Table II. As expected, Hb A_2 levels were significantly increased in β-thalassemia ($p = 0.003$). None of the group differences among the remaining parameters is significant. Although the mean values for each group were in the anemic range, there were individual patients who had a normal hematocrit and hemoglobin level. Anemia is not a prerequisite of thalassemia. The range of values was hematocrit 31.7 to 37.5 and hemoglobin 9.8 to 12.2 in α-thalassemia and hematocrit 28.0 to 37.7 and hemoglobin 8.9 to 12.3 in β-thalassemia. There was a trend for α-thalassemic patients to be less anemic than those with β-thalassemia but this was significant only during the second trimester (Table III). It is apparent that a complete blood count with red blood cell indices cannot differentiate between α- and β-thalassemia during pregnancy.

Contrary to the findings of Pakes and co-workers,[48] our pregnant thalassemic patients had higher red blood cell counts than their hematologically normal counterparts. The expected physiologic hemodilution of pregnancy was observed as a tendency for the hematocrit, hemoglobin, and red blood cell counts to fall after the first trimester; however, this trend did not achieve statistical significance. No such decline was noted for red blood cell indices; the MCV and MCH actually increased between the first and third trimesters. For patients with α-thalassemia trait the first-trimester and third-trimester MCV's and MCH's were 68.1 versus 69.8 fl ($p = 0.013$) and 21.9 versus 22.8 gm/dl of red blood cells ($p = 0.003$), respectively. For β-thalassemic patients the values were 67.8 versus 70.8

fl ($p = 0.068$) and 21.6 versus 23.4 gm/dl of red blood cells ($p = 0.10$). This may be attributable to increased release of immature cells into the circulation as the total red blood cell volume expands during pregnancy. Pakes and associates[48] found that reticulocyte counts were higher in thalassemic patients throughout pregnancy.

In agreement with other investigators, we found no evidence to support Hocking and Ibbotson's[49] supposition that pregnancy presented an overwhelming hematologic stress to the thalassemic patient's defective erythropoietic system. While 36% of their patients received blood products, none of our patients required transfusions, including those undergoing cesarean section. Although megaloblastosis secondary to folate deficiency may complicate β-thalassemia major, it is rarely associated with thalassemia minor.[46] All of our clinic patients routinely receive prenatal vitamins with folate, thus avoiding the possibility of this deficiency. Fleming and Lynch[46] have suggested that increasingly ineffective erythropoiesis and/or hypersplenism might contribute to the decline in hemoglobin levels seen between the first and second trimesters in thalassemic patients. Since the mean decrease in hemoglobin level (0.52 grams) was less than that reported for normal pregnancies (1.6 grams between the twelfth and twenty-sixth weeks[50]), we find no reason to invoke mechanisms in addition to the normal hemodilution of pregnancy.

Pregnancy variables. Maternal age, parity, gravidity, and the number of previous spontaneous abortions, therapeutic abortions, stillbirths, and neonatal deaths did not differ between α- and β-thalassemic patients. Furthermore, these values were comparable to those of the control population. The number of previous stillbirths (three) was greater than normally expected; however, two of these occurred in one woman who also had had three spontaneous abortions. Our results agree with those of Pakes and colleagues[48] who found no impairment of fertility in patients with thalassemia.

The influence of thalassemia on pregnancy was examined and the outcome of 38 pregnancies is shown in Table IV. Four patients remain undelivered. Comparisons between α- and β-thalassemia and between thalassemic and control populations revealed no differences in method of delivery, birth weight, placental weight, fetal/placental ratio, gestational age, or fetal size for age (using Lubchenko's criteria).

When defined as a gestational age ≤37 weeks, six infants (15.4%) were premature. However, only three of these infants weighed under 2,500 grams. The largest infant weighed 3,960 grams with a 700 gram placenta. Unlike previous studies[51, 52] we did not find an increase in placental size.

Fetal outcome. With the exception of one unexplained 300 gram stillborn infant, there were no deaths. Fetal distress was assessed by Apgar scores. Scores were comparable to those of control subjects: 12.8% of 1 minute and 5.1% of 5 minute Apgar scores were less than 7 (control values 15.0% and 4.6%). Thirty-four of the 38 newborn infants were entirely healthy. There were three complications: an imperforate anus, a mild case of idiopathic respiratory distress syndrome at 35 weeks' gestation, and one episode of mild intrapartum asphyxia. It appears that maternal thalassemia does not adversely affect the fetus.

Five neonates at risk for α-thalassemia had cord blood hemoglobin electrophoreses and two had elevated Hb Barts levels. One additional infant, not initially sampled, was later shown to have the α-thalassemia trait. We did not test for the presence of β-thalassemia at birth since this would require synthesis studies but two infants were evaluated when they were over 1 year of age and were found to have β-thalassemia trait. All five thalassemic heterozygous fetuses were healthy newborn infants. There was no instance of a fetus homozygous for thalassemia.

Early investigations concerning the effect of thalassemia on pregnancy indicated that there was a higher incidence of fetal distress and perinatal death. Women with hemoglobin levels less than 10 gm were reported to have a 25% incidence of subnormal estriol excretion[53] and a 5.4% greater incidence of low-birth-weight infants.[54] These adverse effects were attributed to fetal hypoxia secondary to maternal anemia, which in turn resulted in placental hypertrophy.[52] Beischer and associates[51] found approximately twice the normal incidence of placentas weighing over 700 grams.

Our findings agree with more recent observations which demonstrate no increase in prematurity, fetal distress, or perinatal deaths.[48] We did not encounter the prolonged labor and excess blood loss noted by Beaven and coworkers.[55] Although in our experience placentas were of normal size with a normal fetus/placenta ratio, our inability to correlate placental and fetal weight in 22 pregnancies might support Fleming and Lynchs'[46, 52] view that the balance between fetal and placental growth is disturbed by thalassemia. Our patients had hemoglobin levels slightly higher than those in earlier series, perhaps partially accounting for the difference in neonatal results.

Screening results. There has been a substantial increase in the number of thalassemic patients delivered in our hospital. This increase is almost entirely due to detection of patients by the screening program. Of the 33 patients observed during the past 8 years, 21 cases were diagnosed by screening. Over the 5½ years pre-

ceding the program only seven cases (nine pregnancies) were detected. This represents a sixfold increase in the rate of detection. In addition, four heterozygous patients delivered before the institution of screening were identified only when a subsequent screened pregnancy was evaluated. Two thirds of the cases diagnosed by screening were β-thalassemia; one third was α-thalassemia. Prior to implementing our program we had not recognized a single case of α-thalassemia.

Paternal screening. In 50% of the pregnancies the father was also evaluated for thalassemia. Only four of 33 fathers refused screening, but an additional 10 were not assessed due to either physician or paternal inaction. In the years preceding the program only a single father was evaluated.

Fetal risk. Two couples were found in which both parents were heterozygous for thalassemia, thus putting the fetus at risk for homozygous disease. One couple was at risk for a fetus with α-thalassemia, and a prenatal diagnosis of α-thalassemia trait was made and confirmed at delivery. The second couple, heterozygous for β-thalassemia, had two deliveries. The paternal status was unknown during the first pregnancy, which resulted in a 300 gram stillborn infant. The father was not screened until late in the second trimester of the second pregnancy, making it impossible to offer antenatal diagnosis. Fortuitiously, the offspring was found to have only β-thalassemia trait. A third couple was found to have a fetus at risk for sickle-thalassemia disease. The patient declined antenatal diagnosis and is as yet undelivered. Since the status of both partners was known in only 57.5% (19/33) of couples, these three pairs comprised 15.8% (3/19) of examined couples. Over all there was a 0.5% incidence of thalassemia in our prenatal clinic. The percentage of pregnancies at risk for the homozygous state is much less, but 10% of the fathers screened were carriers for the same trait as their spouses.

Ethnic background. Although generally considered a disease affecting peoples of the eastern hemisphere, there is a significant incidence of thalassemia in the United States. A previous study of Greek Americans revealed a 5.0% incidence of β-thalassemia trait and a 2.4% incidence of α-thalassemia trait.[45] In a Canadian prenatal clinic 10.5% of Greek patients were found to have β-thalassemia trait.[48] Thalassemia is one of the most frequent hematologic abnormalities in black Americans with a reported incidence of 1.4% and 5.7% for β- and α-thalassemia traits, respectively.[56] In our experience no ethnic group is exempt from the risk of thalassemia, including those of northern European ancestry.

Comparison of screening methods. It is insufficient to evaluate only patients found to be anemic. Many of our patients with thalassemia trait (α or β) were only mildly anemic and some had normal hematocrit and hemoglobin levels. Therefore, our program uses the simple discriminant MCV < 80 as the initial screening index. In order to evaluate alternative discriminants we applied the Healy, England-Fraser, Mentzer, and Shine-Lal formulas to our thalassemia population.

During the first trimester the Healy and England-Fraser indices each detected 10 of 25 patients (40%) when values less than 1 were considered. During the second trimester the Healy index identified only three patients while the England-Fraser–derived function detected a single patient. The Mentzer index selected nine and three patients during the first and second trimesters, respectively. The Shine-Lal formula was superior to all others. It failed to detect only two cases during the first trimester. The sole case missed by this formula during the second trimester had a MCV > 80 and thus would have escaped detection by our screening program as well. Although previously microcytic, this patient's red blood cell indices had become normal after she developed systemic lupus erythematosus and began releasing immature cells into the peripheral blood. All patients detected had Shine-Lal values < 1,390 (means 1,065 first trimester and 1,118 second trimester). We do not know whether there were cases not recognized by our program which might have been noted by the Shine and Lal function. There were no significant differences in values or rates of detection between α- and β-thalassemic patients using any of the methods.

None of the proposals for screening found in the literature are recommended by their authors for use during pregnancy; our results support this. The Healy, England-Fraser, and Mentzer discriminants failed to detect the majority of thalassemic patients. All are affected by the hemodilution that occurs physiologically during pregnancy. In the presence of concomitant iron deficiency the diagnosis of thalassemia is frequently missed. However, the more recent proposal by Shine and Lal does appear to be useful during pregnancy.

Summary

While in the past the specific diagnosis of thalassemia trait has satisfied the intellectual curiosity of the physician, prevented the useless prescription of iron, and allowed genetic counseling for future pregnancies, a correct prenatal diagnosis was of no urgency. The advent of prenatal diagnosis of thalassemia makes such a casual attitude inappropriate. Homozygous thalas-

semia is a lethal condition. Each year 100,000 children die of β-thalassemia worldwide.[57] The fetus who is homozygous for α-thalassemia is inevitably stillborn. To continue a pregnancy destined to a tragic outcome is unacceptable to most couples when the alternative of prenatal diagnosis and selective abortion is available.

We have instituted a screening program (Fig. 1) which requires little additional cost, but rather an increased awareness of the implication of routine laboratory test results. Since implementing the program we have had a sixfold increase in the number of thalassemic patients detected. This does not appear to be due to an increase in the frequency of the disorder but rather to detection and appropriate evaluation of each patient with microcytosis. Indeed, prior to our program we had not recognized a single case of α-thalassemia trait. During the past 2½ years we have discovered eight such patients who previously would have gone unnoticed or would have been incorrectly diagnosed as iron deficient. In addition, we have encountered four β-thalassemic patients observed at our clinic for previous pregnancies during which time the diagnosis was unsuspected, further supporting our contention that the increased detection rate is attributable to screening.

Our findings indicate that thalassemia occurs more frequently than was previously suspected, but it is still an uncommon disease. Although most clinics will be able to detect couples at risk for having thalassemic infants, it is unlikely that all will generate sufficient volume to provide the experience necessary for accurate and safe prenatal diagnosis. We recommend that such couples be referred to centers which have the necessary expertise in in utero diagnosis.

At our institution we have established such a referral center. Over a period of less than 3 years we have had the opportunity to evaluate 36 pregnancies at risk for β-thalassemia. Eighteen of these couples had requested antenatal diagnosis because they already had had one or more children affected by homozygous disease. We believe that a thalassemia screening program could have prevented most, if not all, of these unfortunate births. Although in the present study we did not encounter a known instance of homozygous disease in our screened population, in those patients referred for prenatal diagnosis we found six fetuses with homozygous thalassemia among the 34 cases where adequate fetal blood was obtained for study. All six pregnancies were terminated at parental request and the diagnosis confirmed by the absence of β-chains and Hb A in the cord blood. Similarly, one instance of homozygous α-thalassemia was found among five sampled pregnancies and terminated.

Thus far, there has been a single factor limiting the effectiveness of our program—inadequate patient education. We are unable to offer fetal prenatal diagnosis to patients if they do not seek prenatal care sufficiently early to terminate the pregnancy, should this be indicated. Similarly, a diagnosis of thalassemia in the mother is of little value unless her partner also understands its implications and agrees to an evaluation. Paternal participation may be facilitated by providing diagnostic evaluation at times other than usual working hours. Of course those patients who find selective abortion unacceptable may not wish to participate in the program. However, we find most patients are interested in the diagnosis and anxious to participate.

Thalassemia is one of the few nongynecologic diseases for which the obstetrician will most likely be the first to make the diagnosis. Over 85% of our cases were diagnosed by the obstetrician. Unlike the rest of the medical community who can attempt only to minimize the suffering which accompanies the homozygous state, the obstetrician-gynecologist can now prevent its occurrence. For both humanitarian and economic reasons, antenatal thalassemia screening is recommended.

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Maternal and amniotic fluid steroids throughout human pregnancy

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Concentrations of testosterone, dihydrotestosterone, androstenedione, progesterone, 17α-hydroxyprogesterone, and estradiol were measured by radioimmunoassay in the amniotic fluid and maternal peripheral blood obtained from normal pregnancies between 14 and 40 weeks of gestation. There was a sex difference in the levels of all the androgenic steroids in the amniotic fluid before 20 weeks with higher levels in pregnancies with male fetuses. Amniotic fluid 17α-hydroxyprogesterone levels were significantly elevated in a pregnancy with the fetus affected with congenital adrenal hyperplasia. The levels of all the steroids in the amniotic fluid were significantly elevated in the pregnancy with molar degeneration of the placenta. There was a sex difference in the levels of dihydrotestosterone in the maternal peripheral blood before 20 weeks with higher levels in pregnancies with male fetuses. There was no correlation between the steroid levels in the maternal serum and amniotic fluid even though most of the samples of maternal serum were drawn at the same time as amniocentesis. (AM. J. OBSTET. GYNECOL. 134:674, 1979.)

PREVIOUS studies on the endocrine function of fetal gonads show that human fetal testis in contrast to ovary secretes significant amounts of testosterone at the period of sexual differentiation in utero.[1, 2] Jost,[3] by his experiments on fetal rabbits, had shown that the development of the male phenotype, except for regression of the müllerian system, depends on the secretion of testosterone by the fetal testis at this critical period. It is also clear from the work of Wilson and Lasnitzki[4, 5] that testosterone itself is responsible for the differentiation of wolffian duct into epididymis, vas differens, and seminal vesicle, and dihydrotestosterone is probably the intracellular mediator in the differentiation of urogenital sinus and urogenital tubercle to prostate and external genitalia. Estradiol does not seem to play a significant role in the process of sexual differentiation and no significant amounts of this steroid had been detected in the fetal testis or ovaries at this stage of pregnancy.[6]

The fetus plays a considerable role in the formation of amniotic fluid in all stages of pregnancy. Before 20 weeks, amniotic fluid possibly bears a closer relationship to fetal plasma in its concentration of the steroids because of the free diffusion occurring through the fetal skin which had been shown by electron microscopy to be a meshlike structure with numerous microvilli.[7] After 20 weeks, fetal urine becomes an important source.[8] The present study was designed to measure various steroids in the amniotic fluid to see whether this approach could be utilized to study the hormonal events occurring in the fetus during different stages of pregnancy. Steroids were also measured in maternal peripheral blood for comparison.

Material and methods

One hundred one samples of amniotic fluid were obtained between 14 and 40 weeks of pregnancy when amniocentesis was done for cytogenetic studies in early pregnancy and for fetal maturity in late pregnancy. All the pregnancies were normal without any complica-

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Table I. Levels of testosterone, androstenedione, dihydrotestosterone, estradiol, progesterone, and 17α-hydroxyprogesterone in the amniotic fluid

Steroids	*14-20 wk.*	*26-40 wk.*
Testosterone (ng/ml):		
M	0.188 ± 0.014* (0.086-0.477)†	0.107 ± 0.015 (0.068-0.172)
F	0.022 ± 0.002‡ (0.006-0.064)	0.056 ± 0.009‡ (0.021-0.132)
Androstenedione (ng/ml):		
M	0.348 ± 0.032 (0.065-0.900)	0.187 ± 0.027 (0.04-0.361)
F	0.156 ± 0.029‡ (0.011-0.810)	0.331 ± 0.038‡ (0.137-0.492)
Dihydrotestosterone (ng/ml):		
M	0.024 ± 0.003 (0.008-0.067)	0.026 ± 0.006 (0.011-0.064)
F	Undetectable	Undetectable
Estradiol (ng/ml):		
M	0.036 ± 0.009 (0.009-0.065)	0.043 ± 0.009 (0.008-0.115)
F	0.048 ± 0.009 (0.011-0.141)	0.067 ± 0.013 (0.018-0.147)
Progesterone (ng/ml):		
M	34.7 ± 4.1 (7-97)	14.1 ± 3.1 (7-31)
F	30.1 ± 4.0 (6-148)	13.3 ± 2.1 (4-20)
17-Hydroxyprogesterone (ng/ml):		
M	1.62 ± 0.15 (0.39-3.23)	0.87 ± 0.15 (0.25-1.25)
F	1.51 ± 0.1 (0.44-2.66)	0.69 ± 0.08 (0.31-1.47)

M = Pregnancies with male fetuses; F = pregnancies with female fetuses.
*Mean levels ± S.E.
†Range.
‡Significantly different from male fetuses.

tions. Fifty-one samples were from pregnancies with male fetuses and 50 samples were from pregnancies with female fetuses. The sex of each fetus was determined at the time of delivery or by karyotype of amniotic fluid cells if undelivered. Seventy-six samples were between 14 and 20 weeks of pregnancy and 25 samples were between 26 and 40 weeks of pregnancy. Additionally, one sample of fluid was obtained from a pregnancy (17 weeks) which ended in an abortion, and the abortus contained a fetus whose karyotype showed triploidy (69, XXX) and extensive molar degeneration of the placenta. There were also four samples of amniotic fluid obtained from different stages of pregnancy in a patient who subsequently delivered a male fetus affected with congenital adrenal hyperplasia (21-hydroxylase deficiency). Sixty samples of maternal peripheral vein blood were obtained from different stages of normal pregnancies. The serum and amniotic fluid samples were stored at −20° C until assayed. Each sample was assayed for testosterone, androstenedione, dihydrotestosterone, estradiol, progesterone, and 17α-hydroxyprogesterone. Fetal age was obtained by subtracting two weeks from the time since the last menstrual period. If the last menstrual period was not known, the length of gestation was determined by ultrasonic measurement of fetal biparietal diameter. Student's t test and Duncan's multirange analysis were used for statistical analysis.

Hormone assays. All the steroids were measured by radioimmunoassay after fractionation of the steroids by Celite microcolumn chromatography as reported earlier.[9] Three milliliters of amniotic fluid or 3 ml of serum was extracted twice with three volumes of ether after adding ^{3}H tracers of progesterone, androstenedione, dehydroepiandrosterone, testosterone, and estradiol for recovery calculations. The extracts were dried under nitrogen and subjected to chromatography on microcelite column with ethylene and propylene glycol as stationary phase. The chromatographic separation was effective in removal of steroids that would interfere in the assay due to cross-reactivity. For example, progesterone and 17α-hydroxyprogesterone; androstenedione, dihydrotestosterone, and testosterone; and estrone and estradiol appeared in separate fractions and estriol was not eluted from the column.[9] The various fractions were collected and dried, and the residue was redissolved in 2 ml of assay buffer. Duplicate aliquots of different volumes of this were used in the assay and 0.1 ml was used for recovery calculations. Blank and control sera (pooled male serum to serve as internal control between assays) were run with each assay. The coefficient of variation between assays had been 5.4% for progesterone, 4.3% for androstenedione, 5.6% for testosterone, 5.8% for dihydrotestosterone, 8.5% for 17α-hydroxyprogesterone, and 8.9% for estradiol. The precision, specificity, and sensitivity for the assay system had been reported previously.[9] ^{3}H-progesterone, ^{3}H-testosterone, and ^{3}H-estradiol were added to amniotic fluid. After extraction, Celite microcolumn chromatography was carried out as previously described with the exception that 1 ml aliquots of the column eluate were collected.

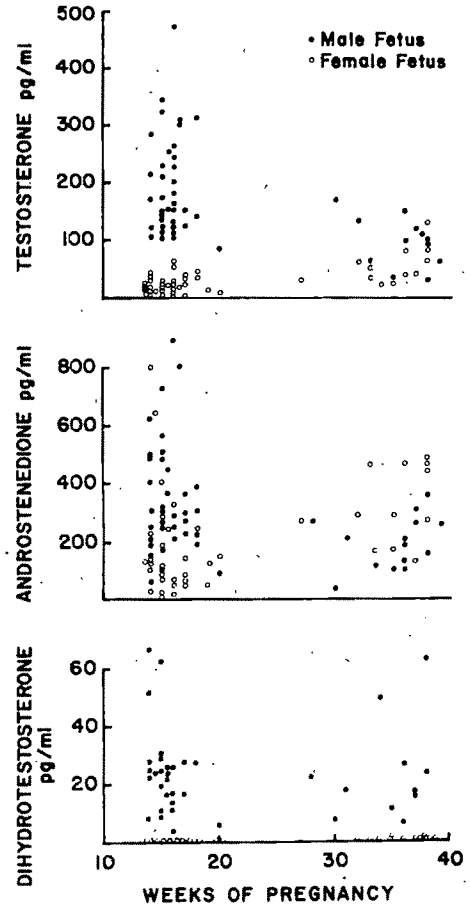


Fig. 1. Concentrations of testosterone, androstenedione, and dihydrotestosterone in amniotic fluid.

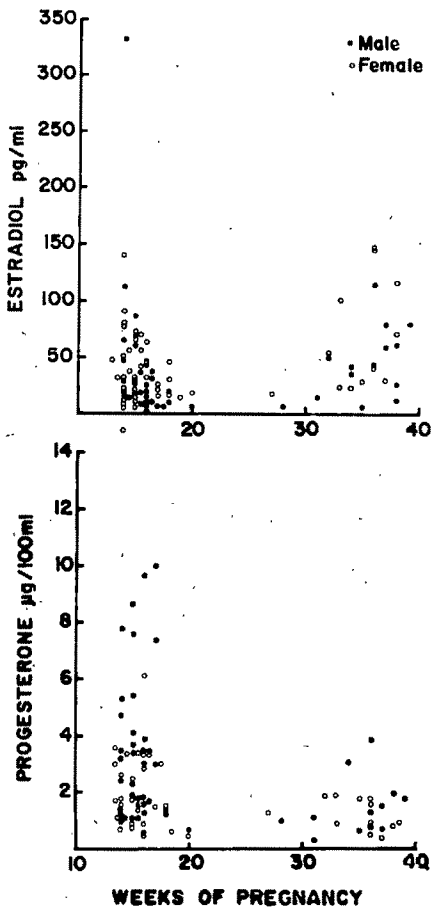


Fig. 2. Concentrations of estradiol and progesterone in amniotic fluid.

There was an excellent correlation between the pattern of radioactivity and immunoassayable material in the fractions in which the above steroids were eluted. Thus, the validation of the method for amniotic fluid was demonstrable.

Results

Amniotic fluid. The mean testosterone concentrations in 101 samples of amniotic fluid are shown in Table I. At all stages of pregnancy, the levels of testosterone were significantly higher when the fetus was male and the difference was significant both in mid-pregnancy and in late pregnancy ($p < 0.001$). Highest levels were noted in the cases of a male fetus at 16 weeks. Between 14 and 20 weeks, the levels of testosterone in pregnancies with male fetuses varied from 0.086 to 0.477 ng/ml (mean 0.188 ± 0.014) and the levels with female fetuses varied from 0.006 to 0.064 ng/ml (mean 0.022 ± 0.002) with no overlap of values (Fig. 1). Toward term, the difference in mean testosterone levels depending on the sex of the fetus persisted, but there was considerable overlap in values (Fig. 1).

The androstenedione levels in the amniotic fluid are also shown in Table I. Between 14 and 20 weeks the levels were significantly higher when the fetus was male than when it was female ($p < 0.001$). Toward term, higher concentrations of androstenedione were present in pregnancies with female fetuses ($p < 0.01$). Although there was a sex difference in the mean levels, there was nevertheless considerable overlap of values between the sexes in all stages of pregnancy (Fig. 1).

Amniotic fluid dihydrotestosterone levels in pregnancies with male fetuses varied from 0.008 to 0.067 ng/ml (mean 0.024 ± 0.003). The levels found between 14 and 20 weeks were not significantly different from those seen close to term. The samples from pregnancies with female fetuses did not have any detectable amounts of dihydrotestosterone (Fig. 1, Table I).

The levels of estradiol in the amniotic fluid are shown in Table I. In all stages of pregnancy, the mean levels were slightly higher in pregnancies with female fetuses than in pregnancies with male fetuses, but the difference was not statistically significant ($p > 0.05$). There was considerable overlap in levels in pregnancies with male fetuses and female fetuses (Fig. 2).

Table II. Amniotic fluid steroids in a pregnancy with a male fetus having congenital adrenal hyperplasia

Weeks of pregnancy	*T (ng/ml)*	*A (ng/ml)*	*DHT (ng/ml)*	*E_2 (ng/ml)*	*P (ng/ml)*	*17α-OHP (ng/ml)*
14	0.22	0.345	0.026	0.106	15	8.23
22	0.606	1.224	—	0.067	15	20.68
28	0.251	0.826	0.040	0.046	20	2.93
34	0.200	—	—	—	—	3.67

Abbreviations: T = testosterone, A = androstenedione, DHT = dihydrotestosterone, E_2 = estradiol, P = progesterone, 17α-OHP = 17α-hydroxyprogesterone.

Table III. Amniotic fluid steroids in a pregnancy with hydatidiform degeneration of placenta

	T (ng/ml)	*A (ng/ml)*	*DHT (ng/ml)*	*E_2 (ng/ml)*	*P (ng/ml)*	*17α-OHP (ng/ml)*
Affected pregnancy	0.129	0.482	0.050	0.466	160.0	6.24
Control	0.022 ± 0.002	0.156 ± 0.029	Undetectable	0.048 ± 0.009	30.1 ± 0.4	1.51 ± 0.1

See Table II for abbreviations.

Progesterone levels in amniotic fluid are shown in Fig. 2 and Table I. The levels were significantly higher ($p < 0.05$) between 14 and 20 weeks than toward term. There was no difference in the levels depending on the sex of the fetus. The 17α-hydroxyprogesterone levels in the amniotic fluid also showed a similar trend with a higher level in early pregnancy ($p < 0.01$; Table I) with no sex difference in the levels.

In the samples of fluid obtained from a patient who subsequently delivered a male fetus affected with congenital adrenal hyperplasia, the concentration of testosterone and androstenedione was higher than the control levels in one sample obtained at 22 weeks, but the levels in other samples were not significantly different from the control levels (Table II). The levels of progesterone, dihydrotestosterone, and estradiol in these samples were within the range of the control samples. However, 17α-hydroxyprogesterone levels were elevated above the control levels in all stages of pregnancy (Table II). The maximum elevation was at 22 weeks of pregnancy.

In the sample of amniotic fluid obtained from a pregnancy in which there was extensive hydatidiform degeneration of the placenta, the level of progesterone, 17α-hydroxyprogesterone, testosterone, dihydrotestosterone, and estradiol were significantly higher than in control samples (Table III). Among the control pregnancies one fetus was found to be mongoloid (trisomy 21) by karyotype of amniotic fluid cells and this pregnancy was subsequently aborted. The steroid levels in the fluid obtained from this pregnancy were within the normal range.

Maternal serum. All the steroids in maternal serum showed progressive increase with increasing duration of gestation. The levels of estradiol varied from 0.6 to 22.6 ng/ml and the levels of progesterone varied from 8.6 to 288.8 ng/ml. Testosterone levels ranged from 0.2 to 3.2 ng/ml with a mean level of 1.01 ± 0.1 ng/ml. Androstenedione levels varied from 1.7 to 21.2 ng/ml with a mean level of 3.29 ± 0.51 ng/ml. The mean levels in pregnancies with male and female fetuses are given in Table IV. We did not find any difference in the levels of these steroids depending on the sex of the fetus. The levels of dihydrotestosterone ranged from 0.04 to 2.02 ng/ml with the mean value of 0.35 ± 0.05 ng/ml. The mean level of dihydrotestosterone in the maternal serum in the pregnancies with male fetuses before 20 weeks was 0.22 ± 0.01 ng/ml which was significantly higher than the mean level of 0.14 ± 0.02 ng noted in pregnancies with female fetuses before 20

Table IV. Levels of steroids in maternal serum

Steroids	*14-20 wk.*	*26-40 wk.*
Testosterone (ng/ml):		
M	0.744 ± 0.08*	0.87 ± 0.2
F	0.935 ± 0.2	1.38 ± 0.3
Androstenedione (ng/ml):		
M	1.87 ± 0.18	3.05 ± 0.9
F	1.6 ± 0.35	6.37 ± 1.8
Dihydrotestosterone (ng/ml):		
M	0.22 ± 0.01	0.42 ± 0.14
F	0.14 ± 0.02†	0.67 ± 0.17
Estradiol (ng/ml):		
M	5.29 ± 0.5	8.26 ± 2
F	4.6 ± 0.6	8.32 ± 2.2
Progesterone (ng/ml):		
M	60.16 ± 9.3	76.73 ± 20
F	51.00 ± 2.4	84.4 ± 24
17-Hydroxyprogesterone (ng/ml):		
M	2.2 ± 0.2	5.2 ± 1.0
F	2.5 ± 0.4	5.6 ± 1.0

M = Pregnancies with male fetus; F = pregnancies with female fetus.

*Mean ± S.E.

†Significantly different from pregnancies with male fetus.

weeks of gestation ($p < 0.02$). There was, however, considerable overlap of values. The concentration of 17α-hydroxyprogesterone in maternal serum before 34 weeks ranged from 0.78 to 4.07 ng/ml with a mean level of 2.6 ± 0.2 ng/ml. There was a twofold increase after 34 weeks with a mean level of 5.4 ± 0.6 ng/ml. The 17α-hydroxyprogesterone level in maternal serum in the pregnancy with the fetus affected with congenital adrenal hyperplasia was significantly higher than the control levels after 34 weeks of pregnancy. The 17α-hydroxyprogesterone levels during pregnancy have been reported by us previously.[25]

Comment

This study compares six steroids in the amniotic fluid of pregnancies with male and female fetuses along with a comparison with steroids circulating in maternal blood. Higher testosterone concentrations in pregnancies with male fetus as compared to female fetus were found with no overlap of values between 14 and 20 weeks of pregnancy. This sex difference persisted in late pregnancy but with considerable overlap of values.

Reyes and associates[10] found significantly higher testosterone levels in the fetal serum when the fetus was male than when it was female. Abramovich and Row[11] found a similar difference in the testosterone concentrations of serum of male and female fetuses between 12 and 18 weeks, but at term there was no significant difference. Our results on amniotic fluid testosterone levels seem to follow the same pattern as that reported for fetal serum. Similar results have been reported recently by Warne and colleagues.[12] Judd and co-workers[13] also found significantly higher levels of testosterone in the amniotic fluid from pregnancies with male fetuses at midterm.

The source of amniotic fluid androstenedione is not very clear. The presence of sex difference in the levels suggests that at least part of this steroid comes from the fetal gonads. In pregnancies with male fetuses we found significantly higher levels of androstenedione between 14 to 20 weeks at which time the fetal testis has been shown to be the site of active steroidogenesis. Robinson and associates[14] have reported similar observations on the sex difference in the levels of androstenedione in midpregnancy. The levels reported by them were three to four times higher than our values. The antiserum for androstenedione used by them was a different one, and no explanation for this difference is available. Close to term, we found significantly higher levels in pregnancies with female fetuses. We are not aware of any report on amniotic androstenedione levels in late pregnancies. Riverola and co-workers[15] did not find any sex difference in the androstenedione levels in the umbilical vein sera of term infants. Payne and Jaffe,[16] by in vitro incubation studies of fetal ovaries with ^{3}H-pregnenolone sulfate, found androstenedione as one of the major C19 metabolite formed by the ovaries, although they failed to detect any estradiol. Fetal adrenals also had been shown to be capable of producing androstenedione.[6]

The third androgen we measured in the amniotic fluid was dihydrotestosterone. Dihydrotestosterone has been shown to be the steroid involved in the differentiation of urogenital sinus to prostate and external genitals. The rate of conversion of testosterone to dihydrotestosterone has been shown to be most rapid in the tissues of urogenital sinus and urogenital tubercle.[1] Significant amounts of dihydrotestosterone were present in the amniotic fluid of pregnancies with male fetuses and it was below the limit of detectability of the assay in the pregnancies with female fetuses. Dawood and Saxena[17] were not able to find any dihydrotestosterone amniotic fluid.

Robinson and colleagues[14] found significantly higher amniotic fluid estradiol concentration in pregnancies with female fetuses at midterm. In addition, the levels of estradiol reported by them were higher than ours. We did not find any significant sex difference in the levels of this steroid and the reason for the discrepancy is not clear at this time. The source of estradiol in the amniotic fluid is still speculative. Payne and Jaffe,[16] by in vitro incubation studies with radioactive precursors, failed to detect any estradiol in the fetal ovaries. Reyes and associates[6] found little or no estradiol in the fetal testis, ovaries, or adrenals. Fetal granulosa cells lacked ultrastructural features associated with steroidogenic activity,[18] and theca interna, a principal source of steroid hormones in the mature ovary, does not differentiate until the follicle development is well established. It seems likely that placenta is probably the principal source of the estradiol in the amniotic fluid.

Progesterone levels in amniotic fluid were higher between 14 and 20 weeks of pregnancy than toward term, with no sex difference in the levels. Our results are comparable to those of Warne and associates[12] with the exception that the decrease in progesterone at term observed by them in pregnancies with male fetuses was not observed by us. Hageman and Kittinger[19] reported that the progesterone concentrations in the umbilical vein were always higher than in the umbilical artery. Billair and co-workers[20] injected ^{3}H-pregnenolone sulfate during midgestation and reported 50% extraction of progesterone by the fetus. Placenta via the fetus is probably the principal source of progesterone in the amniotic fluid. Hageman and Kittinger[19] found that the progesterone concentrations in the umbilical vein at term did not show any sex difference but the umbilical arteriovenous difference at term was higher for fe-

male fetuses than for male fetuses. These authors speculated that the female fetuses seem to metabolize progesterone to a greater extent than male fetuses.

Attempts had been made to diagnose congenital adrenal hyperplasia in utero by measuring different steroids like 17-ketosteroids and pregnanetriol in the amniotic fluid but the results have not been uniform.[21, 22] Frasier and associates[23] have reported that testosterone concentrations in the amniotic fluid from a pregnancy in which the fetus was affected with congenital adrenal hyperplasia were within the range found in control pregnancies. This is in agreement with our results of normal testosterone levels in the affected pregnancy with the exception of the sample at 22 weeks of pregnancy. Measurement of 17α-hydroxyprogesterone levels in the amniotic fluid had been shown to be more promising in the prenatal diagnosis of this disorder.[24, 25]

Previous reports on steroidogenic function of trophoblastic tissue in molar pregnancy are limited. Toeh and co-workers[26] found very high concentrations of progesterone in the mole vesicular fluid. Dawood and co-workers[27, 28] have reported elevated levels of progesterone and estradiol in maternal peripheral blood. Presently we do not have any data available on the levels of androgenic steroids in molar tissue. We found elevated levels of progesterone, estradiol, testosterone 17α-hydroxyprogesterone, and dihydrotestosterone in the amniotic fluid from the pregnancy which ended in an abortion and showed extensive hydatiform degeneration of the placenta (Table III).

The mean level of testosterone in the maternal serum is comparable to the levels reported by other investigations during pregnancy.[29] This increase could be explained by the increased steroid-binding globulin levels during pregnancy and increased binding. The production rate of testosterone during pregnancy had been shown to be not significantly different from the rate seen in nonpregnant state while the metabolic clearance rate is significantly reduced because of increased binding.[30] The level of androstenedione was also higher in the pregnant serum compared to the levels noted in cycling females.[9] Gandy[31] found similar increased levels of androstenedione during pregnancy, while Rivarola and associates[15] did not find any significant increase.

Dihydrotestosterone was also found in higher concentrations during pregnancy than in the nonpregnant state.[9] The production rate of dihydrotestosterone had been reported to be similar in pregnant and cycling women.[31] It is interesting to find increased levels of dihydrotestosterone in the maternal peripheral blood in pregnancies with male fetus than in pregnancies with female fetuses. This raises the possibility that the fetus might be contributing to some of this steroid in the maternal serum. It is hard to explain why this difference did not persist throughout the late stages of pregnancy.

Another steroid in the maternal serum to which the fetus seems to contribute significantly is 17α-hydroxyprogesterone in later stages of pregnancy. This is shown by the fact that increased levels were found in our patient with congenital adrenal hyperplasia and marked fall in levels were noted by Tulchinsky and Simmer[32] in anencephaly and intrauterine death of the fetus.

Our results on the levels of progesterone in the maternal serum are comparable to the levels reported by other investigators.[33, 34] It is fairly well established that placenta is the main site of progesterone production in mid- and late pregnancy.[35, 36] Estradiol is mainly produced by the placenta by way of aromatization of androgenic steroids. Tulchinsky and Korenman[37] found that maternal dehydroepiandrosterone sulfate contributed to 60% of estradiol that is formed during pregnancy. Lindberg and associates[38] measured the estradiol and estriol levels in ten healthy pregnant women and the levels reported by these authors are close to our results.

In conclusion, the maternal compartment does not seem to contribute significantly to the steroids in amniotic fluid since we did not find any correlation between the levels in the maternal serum and amniotic fluid. Several steroids in the amniotic fluid were found in higher concentration in early pregnancy (taking into account the sex of the fetus) while the levels in the maternal serum showed increasing levels with increasing duration of gestation. Since the concentration of steroids found in the amniotic fluid does not correlate with the levels in maternal serum, it leads to the speculation that the fetus is probably the major source of various steroids in the amniotic fluid. There are two possible explanations for the observations of higher concentration of steroids in the amniotic fluid in midpregnancy than in late pregnancy. First, the increased concentrations may indicate increased production of these steroids by the fetus at the critical period of sexual differentiation in midpregnancy. Second, it may be due to the difference in the sources of the amniotic fluid in different stages of pregnancy. In early pregnancy, the steroids possibly enter the amniotic fluid by way of passive diffusion through the fetal skin at which time the steroid levels in the amniotic fluid may closely reflect the levels in the fetal serum. After 20 weeks, the fetal skin gradually becomes thick and cornified and fetal urine becomes an important source. Studies are now underway to correlate the steroid levels in umbilical cord blood and amniotic fluid.

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Effect of stress during labor on the concentration of cortisol and estriol in maternal plasma

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The effect of stress during labor on the plasma concentration of cortisol, unconjugated estriol, and human chorionic somatomammotropin was studied in 15 healthy primiparous women. According to the method of pain relief the parturients were divided into two groups. One group was given continuous epidural analgesia and the other group received pethidine, diazepam, and nitrous oxide/oxygen in response to pain. In the most stressed nonepidural group there was a significant rise in the cortisol level during labor and the estriol concentration fell significantly. In the epidural group no significant changes were observed with respect to the concentration of either cortisol or estriol. These results give further support to the hypothesis that severe maternal stress may lead to a reduced concentration of estriol in maternal plasma. (AM. J. OBSTET. GYNECOL. 134:681, 1979.)

DETERMINATION of unconjugated estriol in maternal plasma has gained wide acceptance as a fetoplacental function test.[1] Fetoplacental insufficiency, however, is not the only factor influencing the estriol production. For instance, it has been shown that administration of corticosteroids to the mother leads to a marked suppression of the synthesis of estriol precursors.[2]

Stress during labor is known to stimulate the maternal hypothalamic-pituitary-adrenal axis.[3] This leads to an increased concentration of cortisol in maternal plasma. The present study was undertaken to see if pain-induced stress during labor is of importance for estriol production. The cortisol-estriol levels were determined during pain-free labor with the use of continuous epidural analgesic drugs as well as during labor with partial relief of pain by conventional central-acting analgesic drugs.

Material and methods

Fifteen healthy primiparous patients (21 to 37 years old) were studied during spontaneous labor. The gestational ages varied from 37 to 42 weeks. All pregnancies were uncomplicated and the study was restricted to labors starting in the morning. Oxytocin was not given. Informed consent was obtained before patients entered the study. Due to ethical reasons strict randomization was omitted. All patients knew and had chosen the method of analgesia to be utilized. The eight patients in the nonepidural group (conventional analgesia) received pethidine, 100 mg intramuscularly, as a single agent or in combination with diazepam, 10 mg orally. A 50/50 mixture of nitrous oxide and oxygen was available for self-administration. A transvaginal pudendal block was given during the second stage of labor. One of the patients did not accept central-acting analgesic or sedative drugs.

The seven parturients in the epidural group received a continuous epidural analgesic drug according to our standard technique[4] early in the first stage of labor. Bupivacaine without adrenaline (Marcain, A/B Astra), 0.25%, was injected into the epidural space through an indwelling catheter. The initial dose of bupivacaine was 25 mg. Top-up doses varying from 12 to 25 mg were administered according to the need of each patient. Other analgesics or sedatives were not given.

The mean duration of labor (from admittance to delivery) was about 14 hours in both groups (range 8 to 19 hours). All neonates were healthy with Apgar scores of 9 or 10 at 5 minutes. Birth weight and placental weight were within normal ranges.

Blood samples for determination of estriol, cortisol,

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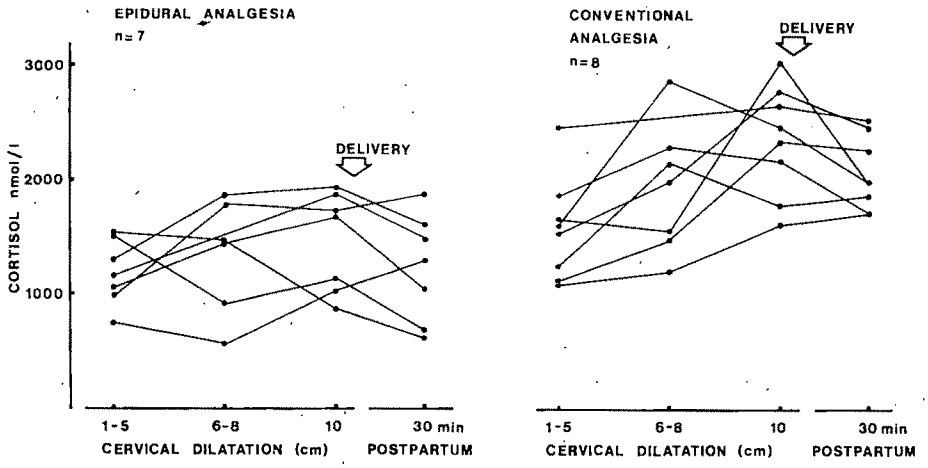


Fig. 1. Plasma concentration of cortisol at different stages of labor. Left: Patients receiving continuous epidural analgesic drug. Right: Patients receiving conventional analgesic drug.

Table I. Maternal plasma concentration of estriol and cortisol in the epidural group and in the nonepidural group (conventional analgesia); values are given as mean ± SD

	Cervical dilatation		
	1-5 cm	*6-8 cm*	*10 cm*
Estriol (nmol/L):			
Epidural	47 ± 16	51 ± 15	45 ± 14
Nonepidural	43 ± 9	36 ± 8*	29 ± 12†
Cortisol (nmol/L):			
Epidural	1,186 ± 284	1,367 ± 451	1,465 ± 443
Nonepidural	1,644 ± 433	2,050 ± 465	2,452 ± 412‡

*Significance of difference from the initial level: $p < 0.02$
†Significance of difference from the initial level: $p < 0.01$
‡Significance of difference from the initial level: $p < 0.05$

and human chorionic somatomammotropin (hCS) were drawn from an antecubital vein into heparinized tubes at the following stages: (1) at a cervical dilatation of 1 to 5 cm, (2) at a cervical dilatation of 6 to 8 cm, (3) at a cervical dilatation of 10 cm, and (4) 30 minutes after delivery.

The first sample in the epidural group was taken before the analgesic drug was administered. Plasma was immediately separated from the corpuscles and stored at −20° C until analyzed.

Hormone analyses. All samples were run in duplicate, and the complete series of samples from one patient was analyzed in the same run. The concentration of unconjugated estriol in plasma was determined by radioimmunoassay principally according to the method of Goebelsmann and associates.[5] Own antiserum directed against 6-keto-estriol 6-carboxy-methoxime: bovine serum albumin was used. No chromatographic purification of the diethyl ether extract was performed since cross-reaction with other steroids was insignificant. The coefficient of variation (CV) (between assays) for estriol analysis was 10%. Cortisol in plasma was determined by double-antibody radioimmunoassay technique with reagents purchased from Diagnostic Products Corporation. The CV of the analysis was 8%. The plasma concentration of hCS was determined by the HPL immunoassay kit supplied by The Radiochemical Centre, Amersham, England; the CV was 7%.

Statistical method. The Wilcoxon two-sample test was used.

Results

Cortisol. The concentration of cortisol in each patient at the different stages of labor is shown in Fig. 1. Table I gives the statistical data. In the "stressed" nonepidural group there was a significant increase in plasma cortisol level from the initial value early in labor to the second stage ($p < 0.05$). Two of the patients in this group had suffered some pain before the first blood sample was obtained. This is reflected in a high initial concentration of cortisol, especially in one of these patients.

In the epidural group there was a slight and insignificant increase in cortisol. In two of the parturients there was an actual fall in cortisol concentration during labor. None of the parturients who received the epidural analgesic drug had been noticeably stressed before entering the study.

Estriol. Fig. 2 shows the concentration of unconjugated estriol in maternal plasma at the different stages. The statistical data are given in Table I.

During labor there was a significant fall in estriol

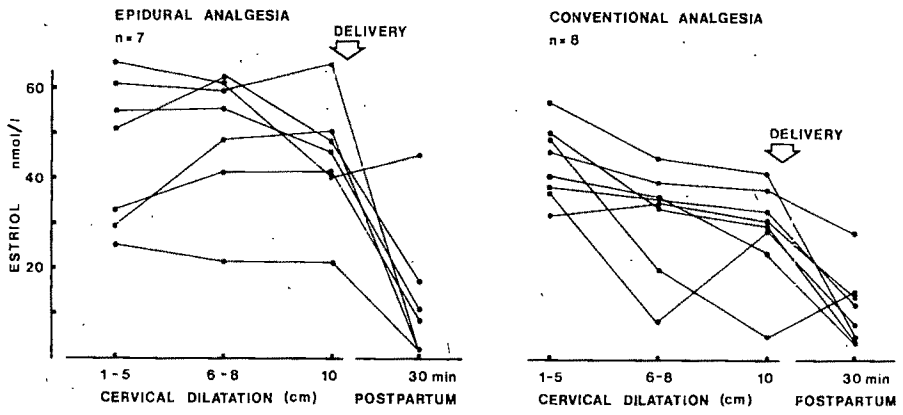


Fig. 2. Plasma concentration of unconjugated estriol at different stages of labor. Left: Patients receiving continuous epidural analgesic drug. Right: Patients receiving conventional analgesic drug.

($p < 0.01$) in the nonepidural group. In the "unstressed" group the range was wider and the changes less consistent. The mean values at the different stages of labor were, however, almost constant. Statistical analysis revealed no significant influence on the estriol concentration in the epidural group.

Determination of hCS was introduced as a parameter of the placental function. The plasma concentration was within the normal range and there was no significant difference between the two groups.

Comment

During labor and delivery a considerable rise in the production of cortisol may occur, usually more marked in primiparous than in multiparous patients.[6] Pain is one of the several stimuli known to initiate such a rise.[7] In a recent study[8] we have shown that the intramuscular administration of a single dose of a synthetic corticosteroid (betamethasone, 12 mg) leads to a more than 50% reduction in the estriol concentration in maternal plasma within 4 hours. This effect may be due to cortisol inhibition of the synthesis of fetal adrenocorticotropic hormone (ACTH), subsequently reducing the production of estriol precursors, mainly 16α-hydroxydehydroepiandrosterone in the fetal adrenal cortex.[9]

In the present study the two groups of patients differed from each other only with respect to the type and efficiency of pain relief. In other respects the groups were very similar, including the placental function as judged by the concentration of hCS.

A considerable difference in the cortisol response during labor and delivery was observed. In the "stressed" nonepidural group there was a marked and significant rise in the cortisol level. In the epidural group, however, only a slight and nonsignificant rise was observed. This is in concert with the results presented by Thornton and associates[7] who found that continuous epidural analgesia was able to block the adrenocortical response to stress only to a certain extent.

A fall in the concentration of unconjugated estriol was observed in every patient in the nonepidural group. In fact, the patient with the highest cortisol value also displayed the lowest estriol level. In the epidural group no significant change was observed in the estriol concentration. In a similar study Okada and colleagues[10] also found a significant increase in cortisol during labor, whereas the decreases in the plasma concentration of estriol was not significant ($p > 0.05$). In our study, however, a significant fall in estriol was observed in the stressed group ($p < 0.01$). The difference between these two studies may be due to differences in parity, in the duration of labor, and in the type of analgesia.

Simmer and associates[2] found that administration of 150 mg cortisol intravenously in three divided doses led to a sixfold increase in the plasma concentration of cortisol. This increase was followed by a reduction in maternal plasma concentration of estriol. In our study the parturients being most stressed (the nonepidural group) showed a threefold increase in cortisol as compared to the level seen in normal third-trimester pregnancies.[8] Thus labor may induce a rise in the concentration of cortisol high enough to suppress fetal ACTH production and thereby also estriol synthesis. When pain is relieved by means of epidural analgesia, this effect is less pronounced. The present investigation, therefore, supports the hypothesis that an increased maternal cortisol concentration may suppress the production of estriol. This mechanism has also been suggested as an explanation of diurnal variations of estriol.[11]

The study indicates that severe maternal stress in pregnancy may have to be considered when estriol is used as a fetoplacental function test.

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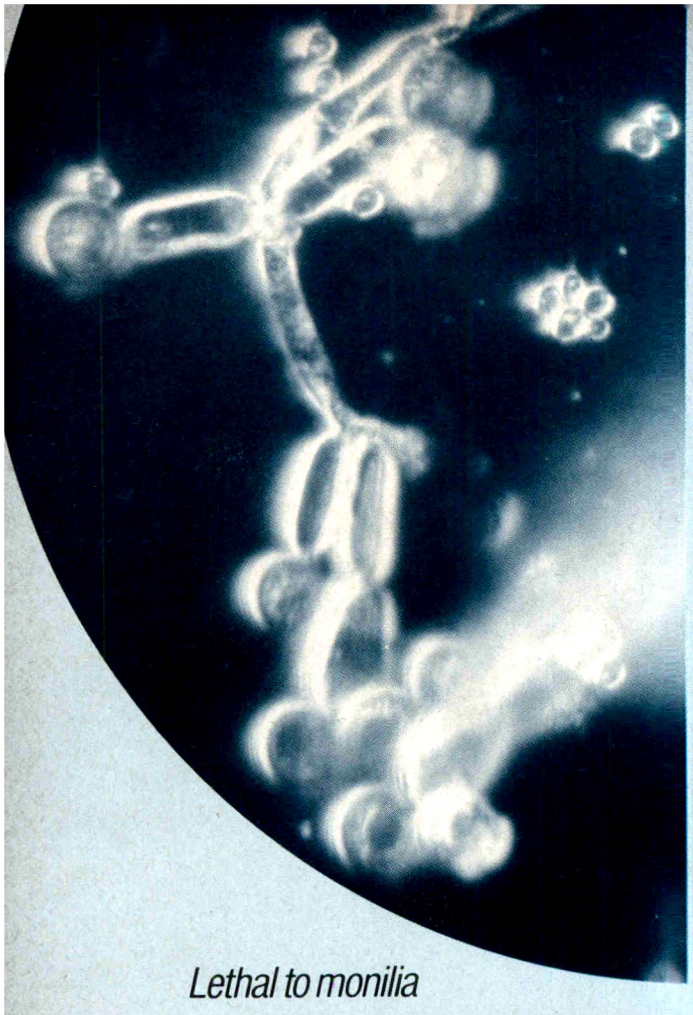
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*BETADINE Vaginal Gel (povidone-iodine) has been evaluated as possibly effective for use in the management of *Trichomonas vaginalis* vaginitis, monilial vaginitis and nonspecific vaginitis.

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See adjoining page for brief summary.

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For douching in the BETADINE Microbicides Vaginitis Regimen, you can now prescribe BETADINE Douche Kit for a complete douching system, or BETADINE Douche 8 oz. for use with a gravity-flow douche bag o bulb syringe.



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For a therapeutic concentration using BETADINE Douche Kit, instruct the patient to: Pour one (1) tablespoonful of BETADINE Douche concentrate into the syringe bottle provided in the kit. Add lukewarm water up *to the top of the syringe bottle.* Attach nozzle and shake gently to mix. Douche, *then repeat the procedure.*

For a therapeutic concentration using BETADINE Douche 8 oz., instruct the patient to: Add two (2) tablespoonfuls to a quart of lukewarm water, for use with a gravity-flow douche bag or bulb syringe.

BETADINE® Vaginal Gel (povidone-iodine) Brief Summary

For use in the treatment of Trichomonas vaginalis vaginitis, monilial vaginitis and nonspecific vaginitis.

Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows: possibly effective for use in the management of trichomonas vaginalis vaginitis, monilial vaginitis and nonspecific vaginitis. Final classification of the less-than-effective indications requires further investigation.

Precaution

If irritation, redness or swelling develops, discontinue use. The rare individual with history of iodine sensitization should not use this product, pending further investigation.

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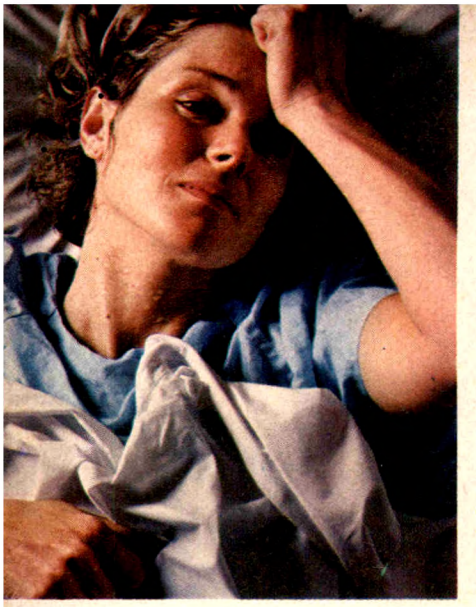
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Although endometrial stimulation is not a concern in the hysterectomized patient, PREMARIN should still be administered cyclically at the lowest effective dose.

PREMARIN. Frequently indicated after surgery...a growing part of the routine.

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(CONJUGATED ESTROGENS TABLETS, U.S.P.)
0.3 mg/0.625 mg/1.25 mg/2.5 mg

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*Conjugated Estrogens Tablets have been evaluated as probably effective for postmenopausal osteoporosis.

See last page of this advertisement for prescribing information.


TERIOR FLA
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BRIEF SUMMARY
(FOR FULL PRESCRIBING INFORMATION AND PATIENT INFORMATION, SEE PACKAGE CIRCULAR)

PREMARIN® Brand of Conjugated Estrogens Tablets, U.S.P.

1. ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA.

Three independent case control studies have reported an increased risk of endometrial cancer in postmenopausal women exposed to exogenous estrogens for more than one year.[1-3] This risk was independent of the other known risk factors for endometrial cancer. These studies are further supported by the finding that incidence rates of endometrial cancer have increased sharply since 1969 in eight different areas of the United States with population-based cancer reporting systems, an increase which may be related to the rapidly expanding use of estrogens during the last decade.[4] The three case control studies reported that the risk of endometrial cancer in estrogen users was about 4.5 to 13.9 times greater than in nonusers. The risk appears to depend on both duration of treatment[1] and on estrogen dose.[3] In view of these findings, when estrogens are used for the treatment of menopausal symptoms, the lowest dose that will control symptoms should be utilized and medication should be discontinued as soon as possible. When prolonged treatment is medically indicated, the patient should be reassessed on at least a semiannual basis to determine the need for continued therapy. Although the evidence must be considered preliminary, one study suggests that cyclic administration of low doses of estrogen may carry less risk than continuous administration;[3] it therefore appears prudent to utilize such a regimen. Close clinical surveillance of all women taking estrogens is important. In all cases of undiagnosed persistent or recurring abnormal vaginal bleeding, adequate diagnostic measures should be undertaken to rule out malignancy. There is no evidence at present that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic doses.

2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY.

The use of female sex hormones, both estrogens and progestogens, during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a non-steroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare.[5,6] This risk has been estimated as not greater than 4 per 1000 exposures.[7] Furthermore, a high percentage of such exposed women (from 30 to 90 percent) have been found to have vaginal adenosis,[8-12] epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether they are precursors of malignancy. Although similar data are not available with the use of other estrogens, it cannot be presumed they would not induce similar changes. Several reports suggest an association between intrauterine exposure to female sex hormones and congenital anomalies, including congenital heart defects and limb reduction defects.[13-16] One case control study[16] estimated a 4.7-fold increased risk of limb reduction defects in infants exposed in utero to sex hormones (oral contraceptives, hormone withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some of these exposures were very short and involved only a few days of treatment. The data suggest that the risk of limb reduction defects in exposed fetuses is somewhat less than 1 per 1000. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well controlled studies that progestogens are effective for these uses. If PREMARIN is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the advisability of pregnancy continuation.

DESCRIPTION: PREMARIN (Conjugated Estrogens Tablets, U.S.P.) for oral administration contains a mixture of estrogens, obtained exclusively from natural sources, blended to represent the average composition of material derived from pregnant mares' urine. It contains estrone, equilin, and 17α-dihydroequilin, together with smaller amounts of 17α-estradiol, equilenin, and 17α-dihydroequilenin as salts of their sulfate esters.

INDICATIONS: Based on a review of PREMARIN Tablets by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications for use as follows:

Effective:

1. Moderate to severe *vasomotor* symptoms associated with the menopause. (There is no evidence that estrogens are effective for nervous symptoms or depression without associated vasomotor symptoms, and they should not be used to treat such conditions.)
2. Atrophic vaginitis.
3. Kraurosis vulvae.
4. Female hypogonadism.
5. Female castration.
6. Primary ovarian failure.
7. Breast cancer (for palliation only) in appropriately selected women and men with metastatic disease.
8. Prostatic carcinoma—palliative therapy of advanced disease.
9. Postpartum breast engorgement—Although estrogens have been widely used for the prevention of postpartum breast engorgement, controlled studies have demonstrated that the incidence of significant painful engorgement in patients not receiving such hormonal therapy is low and usually responsive to appropriate analgesic or other supportive therapy. Consequently, the benefit to be derived from estrogen therapy for this indication must be carefully weighed against the potential increased risk of puerperal thromboembolism associated with the use of large doses of estrogens.[19]

PREMARIN HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING).

"Probably" effective: For estrogen deficiency-induced osteoporosis, and only when used in conjunction with other important therapeutic measures such as diet, calcium, physiotherapy, and good general health-promoting measures. Final classification of this indication requires further investigation.

CONTRAINDICATIONS: Estrogens should not be used in women (or men) with any of the following conditions: 1. Known or suspected cancer of the breast except in appropriately selected patients being treated for metastatic disease. 2. Known or suspected estrogen-dependent neoplasia. 3. Known or suspected pregnancy (See Boxed Warning). 4. Undiagnosed abnormal genital bleeding. 5. Active thrombophlebitis or thromboembolic disorders. 6. A past history of thrombophlebitis, thrombosis, or thromboembolic disorders associated with previous estrogen use (except when used in treatment of breast or prostatic malignancy).

WARNINGS: At the present time there is no satisfactory evidence that estrogens given to postmenopausal women increase the risk of cancer of the breast,[17] although a recent study has raised this possibility.[18] There is a need for caution in prescribing estrogens for women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms. A recent study has reported a 2- to 3-fold increase in the risk of surgically confirmed gallbladder disease in women receiving postmenopausal estrogens.[17]

Adverse effects of oral contraceptives may be expected at the larger doses of estrogen used to treat prostatic or breast cancer or postpartum breast engorgement; it has been shown that there is an increased risk of thrombosis in men receiving estrogens for prostatic cancer and women for postpartum breast engorgement.[19-22] Users of oral contraceptives have an increased risk of diseases, such as thrombophlebitis, pulmonary embolism, stroke, and myocardial infarction.[23-30] Cases of retinal thrombosis, mesenteric thrombosis, and optic neuritis have been reported in oral contraceptive users.[31,32] An increased risk of postsurgery thromboembolic complications has also been reported in users of oral contraceptives.[33,34] If feasible, estrogen should be discontinued at least 4 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization. Estrogens should not be used in persons with active thrombophlebitis, thromboembolic disorders, or in persons with a history of such disorders in association with estrogen use. They should be used with caution in patients with cerebral vascular or coronary artery disease. Large doses (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown[35] to increase the risk of nonfatal myocardial infarction, pulmonary embolism and thrombophlebitis. When doses of this size are used, any of the thromboembolic and thrombotic adverse effects should be considered a clear risk.

Benign hepatic adenomas should be considered in estrogen users having abdominal pain and tenderness, abdominal mass, or hypovolemic shock. Hepatocellular carcinoma has been reported in women taking estrogen-containing oral contraceptives.[36] Increased blood pressure may occur with use of estrogens in the menopause[37] and blood pressure should be monitored with estrogen use. A worsening of glucose tolerance has been observed in patients on estrogen-containing oral contraceptives. For this reason, diabetic patients should be carefully observed. Estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases.

PRECAUTIONS: Physical examination and a complete medical and family history should be taken prior to the initiation of any estrogen therapy with special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolau smear. As a general rule, estrogen should not be prescribed for longer than one year without another physical examination being performed. Conditions influenced by fluid retention such as asthma, epilepsy, migraine, and cardiac or renal dysfunction, require careful observation. Certain patients may develop manifestations of excessive estrogenic stimulation, such as abnormal or excessive uterine bleeding, mastodynia, etc. Oral contraceptives appear to be associated with an increased incidence of mental depression.[23a] Patients with a history of depression should be carefully observed. Preexisting uterine leiomyomata may increase in size during estrogen use. The pathologist should be advised of estrogen therapy when relevant specimens are submitted. If jaundice develops in any patient receiving estrogen, the medication should be discontinued while the cause is investigated. Estrogens should be used with care in patients with impaired liver function, renal insufficiency, metabolic bone diseases associated with hypercalcemia, or in young patients in whom bone growth is not complete.

The following changes may be expected with larger doses of estrogen:

a. Increased sulfobromophthalein retention.

b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.

c. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by PBI, T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered.

d. Impaired glucose tolerance.

e. Decreased pregnanediol excretion.

f. Reduced response to metyrapone test.

g. Reduced serum folate concentration.

h. Increased serum triglyceride and phospholipid concentration.

As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk.

ADVERSE REACTIONS: The following have been reported with estrogenic therapy, including oral contraceptives: breakthrough bleeding, spotting, change in menstrual flow; dysmenorrhea; premenstrual-like syndrome; amenorrhea during and after treatment; increase in size of uterine fibromyomata; vaginal candidiasis, change in cervical erosion and in degree of cervical secretion; cystitis-like syndrome; tenderness, enlargement, secretion (of breasts); nausea, vomiting, abdominal cramps, bloating; cholestatic jaundice; chloasma or melasma which may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair, hirsutism; steepening of corneal curvature; intolerance to contact lenses; headache, migraine, dizziness, mental depression, chorea; increase or decrease in weight; reduced carbohydrate tolerance; aggravation of porphyria; edema; changes in libido.

ACUTE OVERDOSAGE: May cause nausea, and withdrawal bleeding may occur in females.

DOSAGE AND ADMINISTRATION: 1. *Given cyclically for short term use only:* For treatment of moderate to severe *vasomotor* symptoms, atrophic vaginitis, or kraurosis vulvae associated with the menopause (0.3 to 1.25 mg or more daily).

The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible.

Administration should be cyclic (*e.g.* three weeks on and one week off).

Attempts to discontinue or taper medication should be made at three to six month intervals.

2. *Given cyclically:* Female hypogonadism. Female castration. Primary ovarian failure. Osteoporosis.

Female hypogonadism—2.5 to 7.5 mg daily, in divided doses for 20 days, followed by a rest period of 10 days' duration. If bleeding does not occur by the end of this period, the same dosage schedule is repeated. The number of courses of estrogen therapy necessary to produce bleeding may vary depending on the responsiveness of the endometrium.

If bleeding occurs before the end of the 10 day period, begin a 20 day estrogen-progestin cyclic regimen with PREMARIN (Conjugated Estrogens Tablets, U.S.P.), 2.5 to 7.5 mg daily in divided doses, for 20 days. During the last five days of estrogen therapy, give an oral progestin. If bleeding occurs before this regimen is concluded, therapy is discontinued and may be resumed on the fifth day of bleeding.

Female castration and primary ovarian failure—1.25 mg daily, cyclically. Adjust upward or downward according to response of the patient. For maintenance, adjust dosage to lowest level that will provide effective control.

Osteoporosis (to retard progression)—1.25 mg daily, cyclically.

3. *Given for a few days:* Prevention of postpartum breast engorgement—3.75 mg every four hours for five doses, or 1.25 mg every four hours for five days.

4. *Given chronically:* Inoperable progressing prostatic cancer—1.25 to 2.5 mg three times daily.

Inoperable progressing breast cancer in appropriately selected men and postmenopausal women—10 mg three times daily for a period of at least three months.

Patients with an intact uterus should be monitored for signs of endometrial cancer and appropriate measures taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

HOW SUPPLIED: PREMARIN (Conjugated Estrogens Tablets, U.S.P.) No. 865—Each *purple* tablet contains 2.5 mg in bottles of 100 and 1,000. No. 866—Each *yellow* tablet contains 1.25 mg in bottles of 100 and 1,000. Also in unit dose package of 100. No. 867—Each *red* tablet contains 0.625 mg in bottles of 100 and 1,000. Also in unit dose package of 100. No. 868—Each *green* tablet contains 0.3 mg in bottles of 100 and 1,000.

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The relationship of heart rate patterns and tissue pH in the human fetus

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The relationship between different FHR patterns and fetal tissue pH in 68 high-risk gravidas in labor was analyzed. A tissue pH electrode was placed in the fetal scalp and tissue pH recorded on a fetal monitor every 15 seconds along with uterine contractions and continuous fetal heart rate. The tissue pH changes correlated with the FHR patterns in a manner consistent with current concepts of fetal stress. Trend monitoring of fetal tissue pH in labor may prove useful in the management of high-risk patients in labor. (AM. J. OBSTET. GYNECOL. 134:685, 1979.)

PERINATAL MEDICINE has accepted continuous fetal heart rate (FHR) monitoring and fetal scalp blood sampling as an optimal approach to the assessment of fetal well-being in labor. Recent work has demonstrated the feasibility of continuous tissue pH (TpH) measurement in the human fetus during labor.[1, 2] This investigation focuses on the effects of different FHR patterns on the fetal TpH in 68 high-risk patients.

Material and methods

A miniature glass pH electrode with a self-contained reference solution† was utilized, as described by Stamm and associates.[3] The electrode is held in place by a specially designed double-spiral ECG electrode (Fig. 1). This system, connected to a recording device, permits display of the TpH every 15 seconds, along with FHR and uterine contractions. The technique of application begins with the introduction of a modified amnioscope into the cervix with the use of sterile procedure. The fetal scalp is cleansed with Pharmadine,* and a scalp blood sample is obtained in the conventional manner. The spiral ECG electrode is then secured to the fetal scalp with an electrode forceps. The standard pH knife is then used to make a 2 by 2 mm incision in the fetal scalp through the central opening in the ECG electrode. The TpH electrode is then inserted into the fetal subcutaneous tissue through the scalp incision and held in place by the ECG electrode. Periodic scalp blood samples were taken during labor, and at delivery umbilical artery and vein pH were measured as well. All blood pH (BpH) samples were assayed by means of a microanalyzer.†

Results

Continuous pH monitoring was attempted on 68 high-risk patients at 38 to 40 weeks' gestation, in whom

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Table I. Average TpH and BpH with various FHR patterns

FHR pattern	Initial TpH	Initial BpH	TpH during FHR changes	Delivery pH		
				TpH	UA	UV
Tachycardia (5)*	7.26	7.30	7.18	7.21	7.28	7.29
Acceleration (14)	7.26	7.39	7.27	7.24	7.27	7.30
Early deceleration (5)	7.25	7.28	7.25	7.23	7.28	7.30
Variable deceleration (25)	7.25	7.30	7.25	7.23	7.30	7.32
Deceleration, late component (14)	7.23	7.27	7.20	7.23	7.27	7.29
End-stage deceleration (8)	7.26	7.31	7.24	7.24	7.28	7.30
Moderate bradycardia (11)	7.25	7.30	7.25	7.22	7.31	7.32
Reduced variability (11)	7.22	7.27	7.23	7.24	7.28	7.29
Normal (5)	7.25	7.30	—	7.23	7.31	7.32

Numbers in parentheses indicate number of cases.

Table II. Effect of FHR changes on TpH

Pattern	Cases	Increased	Decreased	Unchanged	% decreased
Normal	5	2	0	3	0
Acceleration	14	3	0	11	0
Moderate bradycardia	11	1	0	10	0
Early deceleration	5	0	1	4	20
Variable deceleration	25	0	6	19	25
End-stage deceleration	10	2	1	7	10
Reduced variability	11	0	4	7	36
Deceleration with late component	14	0	13	1	93
Tachycardia	5	0	3	2	60

Table III. Low Apgar scores: comparison of blood and tissue pH

Diagnosis	FHR patterns	Average change with decelerations		Delivery			Apgar
		TpH	BpH	TpH	UA	UV	
Abruptio placentae	Deceleration, late component	−0.03	−0.01	7.20	7.30	7.32	5/7
Toxemia, nuchal cord	Deceleration, late component	−0.02	0	7.38	7.39	7.38	6/8
Amnionitis	Deceleration, late component, tachycardia	−0.05	−0.06	7.19	7.21	7.20	6/9

scalp blood sampling was clinically indicated, and informed consent was obtained. There were 55 cases in which data were in the physiologic range, and these were used for the study.

The TpH usually was lower than the BpH, with the average BpH-TpH difference −0.04 pH units. The data were plotted in a scattergram to compare BpH and TpH by linear regression analysis (Fig. 2). The correlation coefficient is 0.63, $p < 0.01$, a significant positive correlation. Further regression analysis by Spearman's rank correlation coefficient, used for nonrandom distributions such as might be expected for a

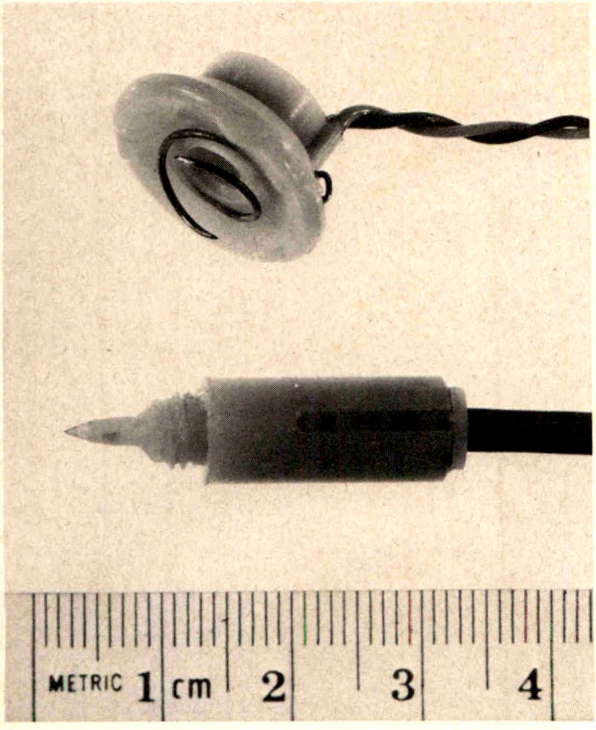


Fig. 1. The ECG electrode is seen above the pH electrode.

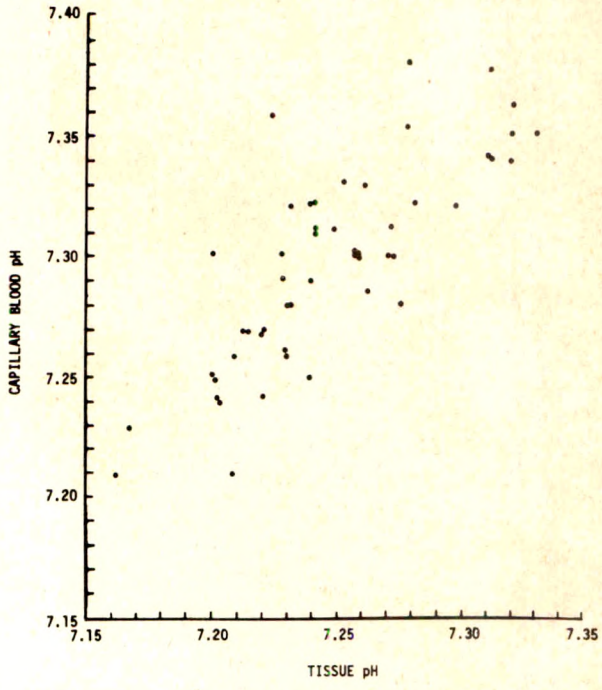


Fig. 2. Tissue pH vs. capillary blood pH in the fetal scalp. The tissue pH is shown on the horizontal scale and the blood pH on the vertical scale.

series of high-risk pregnancies, revealed rS = 0.74, $p < 0.001$, a highly significant correlation. The standard error of the estimate was 0.0354, within the range seen with scalp blood sampling alone.[4, 5] Comparison of umbilical artery and TpH by similar statistical analysis showed r = 0.73, $p < .001$, rs = 0.63, $p < .01$ (Fig. 3).

Uterine contractions were associated with no change or a slight rise in TpH in the absence of FHR changes. There was a relative fall of the TpH as labor progressed, on the order of −0.01 pH units per hour, not seen with BpH. At present it cannot be determined if the fall in the TpH is a real change or due to in vivo drift of the tissue pH electrode, which may occur at rates up to −0.005 pH units per hour. The TpH reflected FHR changes within 2 or 3 minutes (Figs. 4*A*, 4*B*, and 4*C*). The average TpH during the period of FHR change was correlated with the relative pathologic nature of the FHR change (Fig. 5). The lowest average TpH was seen during tachycardia and decelerations with a late component; the highest was seen during accelerations and the normal and relatively benign FHR patterns (Table I). When the effect of FHR changes on TpH in individual cases is considered, the relationships are further elucidated (Table II). TpH changes of 0.02 pH units or greater from the baseline TpH just before the FHR change were considered significant. The TpH changes reflect the relative serious-

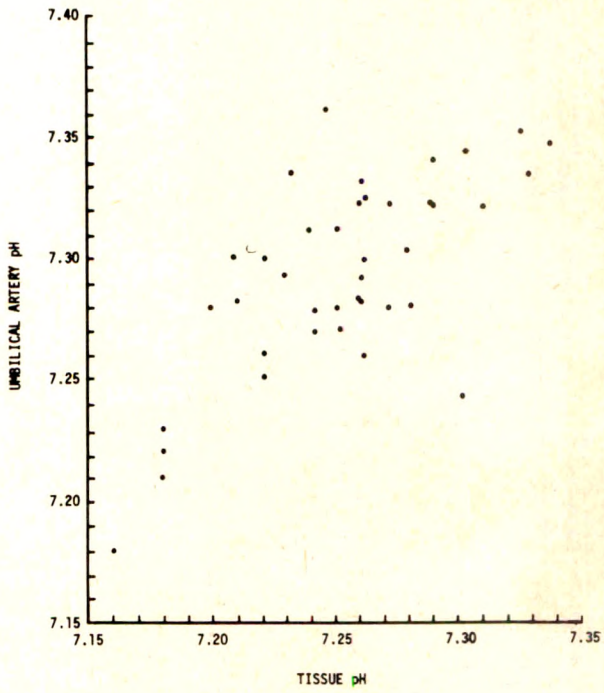


Fig. 3. Tissue pH immediately prior to delivery vs. umbilical artery pH. The tissue pH is shown on the horizontal scale and the umbilical artery pH on the vertical scale.

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Am. J. Obstet. Gynecol.

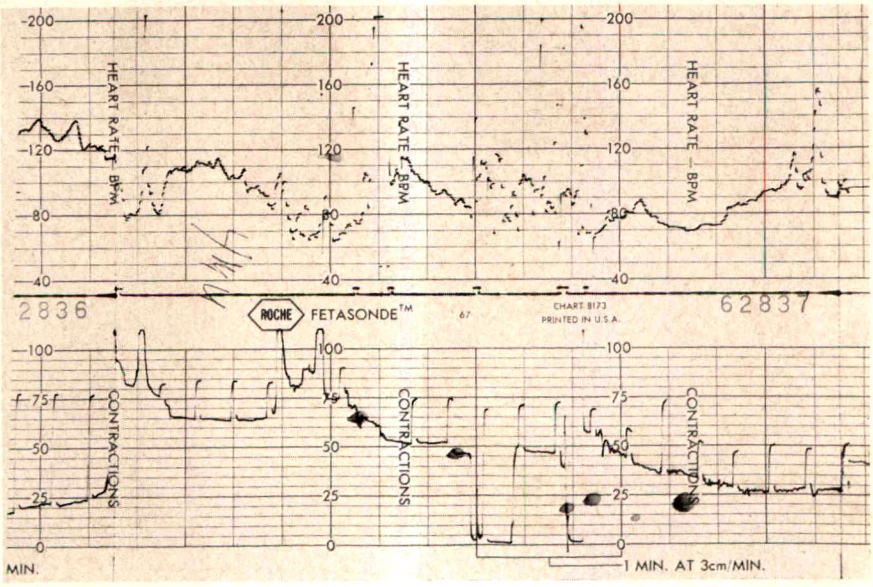


Fig. 4A. Response of TpH to FHR change. The upper portion of this figure and of Figs. 4*B* and 4*C* shows the FHR. The lower channel shows uterine contractions with the tissue pH seen as a bar graph superimposed on the contraction recording. The zero line on the contraction channel equals a pH of 7.00. The 25 line equals 7.10, 50 equals 7.20, 75 equals 7.30, and 100 equals 7.40. Depicted above are severe variable decelerations with late component associated with falling TpH. The pH falls from 7.34 to 7.20

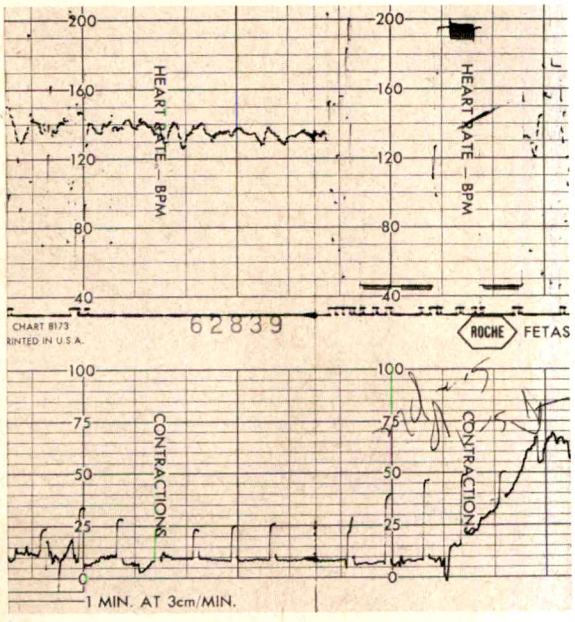


Fig. 4B. See legend of Fig. 4*A*. Bradycardia gradually recovered in 5 minutes. The TpH fell markedly, with peak effect by 10 minutes, declining to 7.10. The FHR artifact seen in the last 2 minutes is due to scalp blood pH sampling.

ness of the FHR pattern. Ninety-three percent of the cases of decelerations with a late component showed a fall in TpH. There were none in the innocent patterns of acceleration and moderate bradycardia, as well as none in the normal patterns without periodic FHR changes.

There were only three cases in which the Apgar scores were below 7 at 1 minute, and none was below 7 at 5 minutes of life. Table III shows that the TpH fell in each case and the BpH fell in two of three cases during the time of FHR change. At delivery, preacidosis levels were seen in two thirds TpH and one third BpH in the cases with low Apgar scores.

Comment

The TpH changes in the cases with low Apgar scores reflected fetal status in a manner at least comparable to the BpH, if not more accurately. TpH is correlated with BpH significantly but averages 0.04 pH units lower in the term human fetus in labor. This difference may be related to changes in calibration with time, inherent errors in the methods, or physiologic factors which may render the tissues more acid than the capillary blood. For example, such factors may be seen in any recent wound, where the initial response to injury is the formation of a relatively acid wound fluid.[6]

Changes in FHR which affect TpH do so within 2 or 3 minutes. Thus, there is a short lag time between the alteration in fetal cardiovascular function and the biochemical responses seen in the TpH. There was a clear relationship between the FHR patterns and the TpH changes. This relationship was consistent with the expected response encompassed by the known pathophysiology of FHR changes. Thus, the greatest incidence of falling TpH was in decelerations with a late component (93%) and fetal tachycardia (60%), whereas

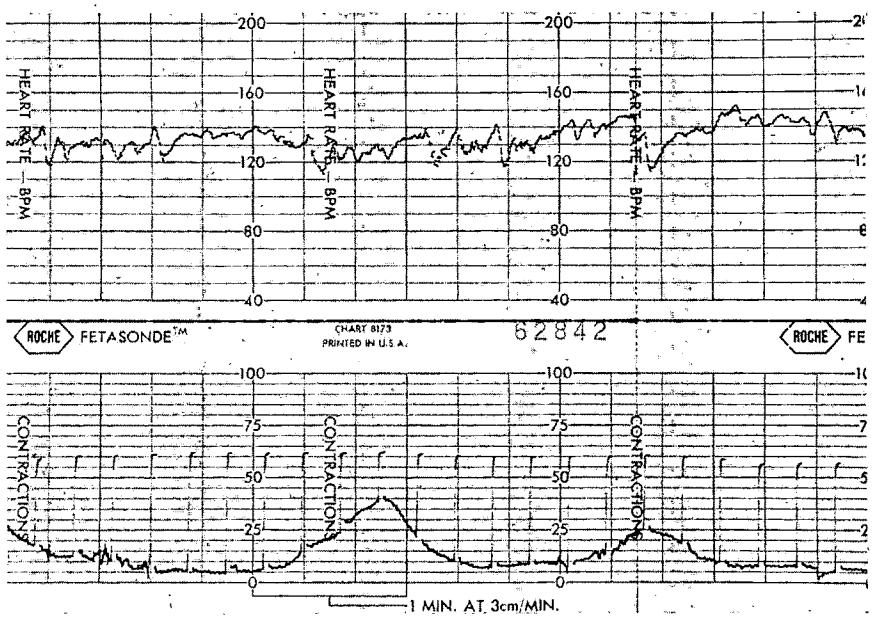


Fig. 4C. See legend of Fig. 4*A*. FHR recovery followed by recovery of TpH. BpH was 7.24 when TpH was 7.22 during recovery phase. Tissue pH has stabilized at 7.24, significantly below the 7.34 prior to the abnormal FHR pattern despite recovery of the FHR 15 minutes earlier.

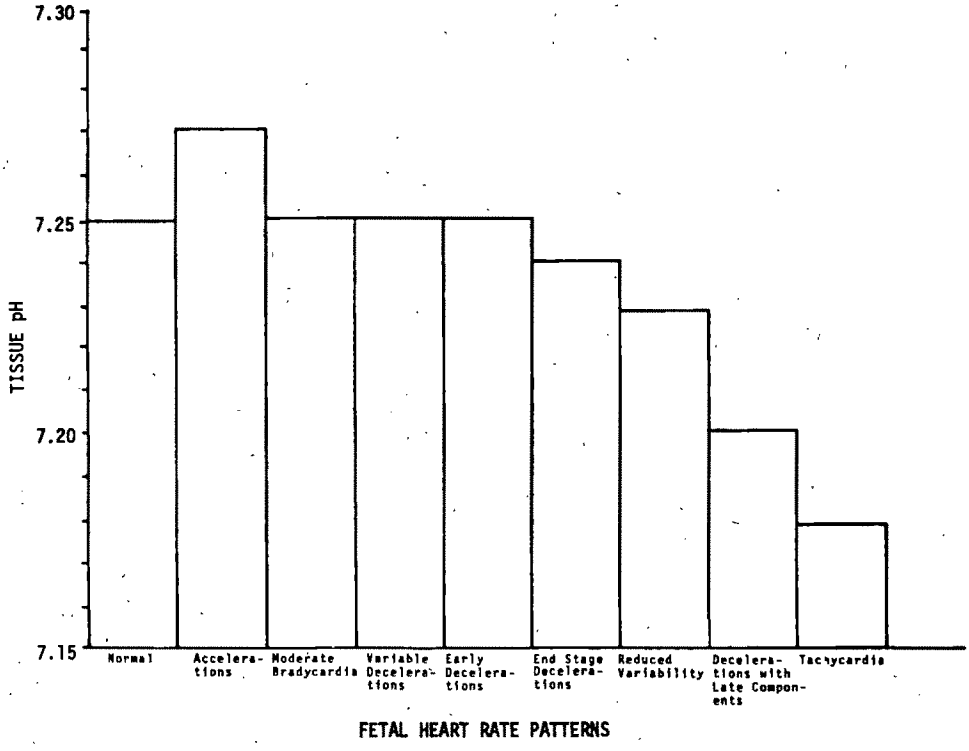


Fig. 5. Average tissue pH with various fetal heart rate patterns. The average tissue pH is shown on the vertical scale. Each bar represents a different fetal heart pattern.

the average TpH was lowest during these FHR patterns. Moreover, the innocuous FHR changes were associated with the highest average TpH and no cases of falling TpH. The TpH changes follow the current concepts of fetal stress responses, although the pathophysiology is not completely clear at present. Continuous TpH trend monitoring offers an additional modality for clinical and investigational interpretation of FHR patterns. Presently it should be considered complementary to the existing methods for evaluating fetal

condition in labor. The pathophysiologic relationships between TpH and BpH remain to be elucidated. The early diagnosis of fetal distress, avoidance of unnecessary cesarean sections, and reduction of fetal and maternal hazards are possible benefits if continuous TpH monitoring proves clinically effective. Further studies are indicated to determine the clinical value of continuous TpH monitoring as part of the optimal care of high-risk pregnancy.

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Fetal heart rate variability: An approach to automated assessment

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Three hundred seventy-five hours of fetal heart rate (FHR) data derived from the direct fetal electrocardiogram (ECG) were studied. This data had been stored on magnetic tape from 83 intrapartum patients. By means of a computerized technique, the FHR variability was assessed quantitatively. The degree of variability was then related to: (1) state of labor, (2) fetal scalp pH values, and (3) the 1-minute Apgar score. FHR variability was computed from differences between consecutive R-R intervals measured from the R wave of each fetal ECG. A trend of increasing variability was seen with advancing labor, defined by either time prior to delivery or cervical dilatation, but values were not statistically significant. Significantly less FHR variability was encountered when fetal scalp pH values below 7.20 were compared to higher values. FHR variability assessed during the 20 minutes immediately preceding delivery was significantly lower in infants with 1-minute Apgar scores less than 7. Machine assessment of FHR variability thus could be correlated with fetal condition as determined by scalp pH and neonatal outcome determined by Apgar score. (AM. J. OBSTET. GYNECOL. 134:691, 1979.)

IN RECENT years, variability of the fetal heart rate (FHR) has become the object of numerous studies and is currently a major focus of physiologic investigation.[1, 2] It is established that a decrease in FHR variability, evaluated visually, may be associated with fetal and neonatal compromise.[3–7]

One of the basic problems which has obstructed understanding and agreement regarding the assessment of variability has been the various instrumentation approaches used to produce a FHR. Thus, the FHR obtained from the phonocardiographic or ultrasonocardiographic signals inherently may present a false picture of variability because of (1) imprecise signal sources and variation, (2) the presence of artifacts, and (3) averaging techniques required to present "reasonable FHR" data from such sources.[8]

The assessment of the actual FHR variability as described in this study requires the direct fetal electrocardiogram (ECG) as a signal source. The interval between each QRS complex is precisely measured from the peak of successive R waves and FHR variability is computed from successive R-R interval differences. The purpose of the study was to relate a new method of machine assessment of FHR variability and to correlate the results of this method with labor advancement, fetal scalp pH, and neonatal 1-minute Apgar score.

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Material and methods

Records from the Perinatal Intensive Care Unit at Los Angeles County–University of Southern California Medical Center, Women's Hospital, were reviewed for

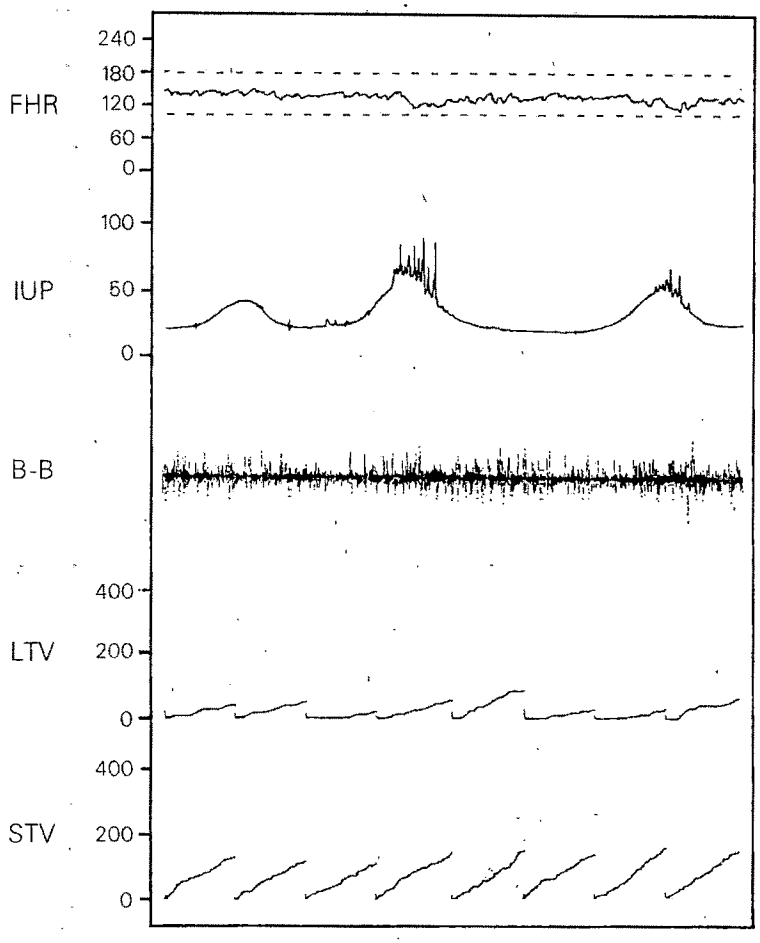


Fig. 1. The 5 channel printout. Channels 1 and 2 contain electrode FHR and internal catheter uterine pressure data. Beat-to-beat variability is displayed on the center channel. LTV and STV are shown on Channels 4 and 5 presented as beat change per 100 consecutive fetal heart beats.

Table I. Obstetric condition

Condition	*No.*
Normal	36
Intrapartum distress	26
Diabetes mellitus, Class B	3
Diabetes mellitus, Class C	2
Postmaturity	7
Toxemia	8
Rh isoimmunization	1
Total	83

suitability for the study. The following criteria were required for inclusion: (1) the original FHR record was of high quality and free of artifact, (2) the record contained significant labor data, such as frequent vaginal examinations, fetal scalp pH values, and immediate neonatal evaluation by a neonatal fellow, (3) the fetus was directly monitored for at least three hours with a vaginal delivery of a term newborn infant, and (4) no medications were administered during the study period or in the hour preceding the study. The selection process purposefully included a larger-than-expected number of newborn infants with low 1-minute Apgar scores. Eighty-three intrapartum patients were studied for 375 hours with the mean duration being 4 hours, 32 minutes (Tables I, II, and III).

Instrumentation. The fetal ECG was obtained with a direct electrode attached to the fetal scalp. Intrauterine pressure was obtained by means of a transcervical, open-ended, fluid-filled catheter inserted into the amniotic sac. All data were recorded on magnetic tape for subsequent study, and long- and short-term variability as subsequently described were derived from these tapes. Fetal blood sampling was accomplished as per the method of Saling[9] and pH determinations were performed using a Radiometer BMS3 microelectrode.

Variability assessment. The calculation of variability used an approach designed by two of the authors (E. H. H. and J. J.). The method was based on the precise measurement of the differences in milliseconds

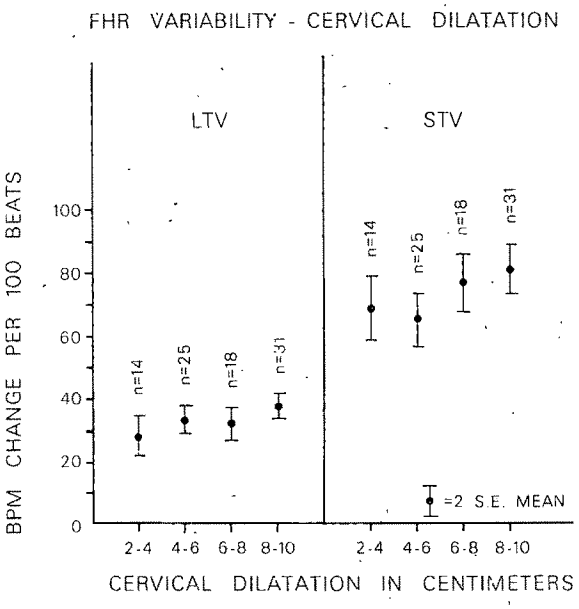


Fig. 2. Variability at progressive cervical dilatation is shown using the standard error of the mean.

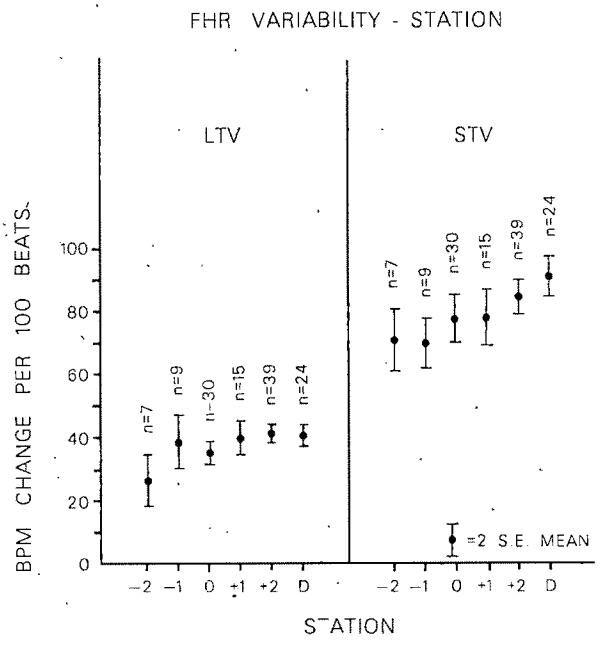


Fig. 3. Mean baseline variability is illustrated at various stations. A progressive increase in variability is seen with descent of the presenting fetal vertex. Statistically significant difference is seen between values at −2 station and those at crowning.

between the consecutive R-R intervals of the fetal ECG. The millisecond R-R interval time was converted to a corresponding beats-per-minute value, i.e., the number of beats in one minute if that R-R interval were maintained for the entire minute. The difference in the beats-per-minute value of each interval and the preceding interval was calculated and given a plus (+) or a minus (−) sign in comparison with the previous interval. For example, an interval shorter than the previous one would have a negative sign, meaning a faster corresponding beats-per-minute rate than the previous interval. The actual change in beats-per-minute (bpm) between each consecutive R-R interval was the value accumulated for the calculation of FHR variability. The sign given each interval, i.e., plus (+) or minus (−) and sign change was used to indicate whether the value or change in rate was calculated as long- or short-term FHR variability. In other words, the sign of each interval difference was compared with the sign of the previous interval and from this, the long- and short-term variability was computed.

Short-term variability was computed by totaling the values from any two consecutive R-R intervals where there was a sign change. Additionally, the second consecutive interval following an R-R interval with a sign change was calculated as short-term variability.

Whenever three or more intervals with identical signs were encountered, this was considered long-term variability. Both long-term and short-term measures were accumulated for 100 consecutive intervals and displayed graphically (Fig. 1). These accumulative values of both long- and short-term variability totaled for each 100 beats are presented as "beats-per-minute change per 100 beats."

Table II. Monitoring duration

1 min. Apgar	*No.*	*Hr. monitored*	*Average/patient*
≥7	36	154	4 hr. 17 min.
<7	47	221	4 hr. 42 min.
Total	83	375	

Table III. Patient distribution by Apgar scores

1 min. Apgar	1	2	3	4	5	6	7	8	9	10
Number	13	12	7	3	5	7	0	9	27	0

Data selection. The FHR variability was calculated continuously, but only variability values obtained during the baseline period of FHR were used. The baseline FHR variability data for each 20 minutes was averaged. The long-term and short-term measures for 20 minute periods of variability were evaluated in relationship to (1) labor progress as documented by both cervical dilatation and station change, (2) fetal scalp pH, and (3) 1-minute Apgar score.

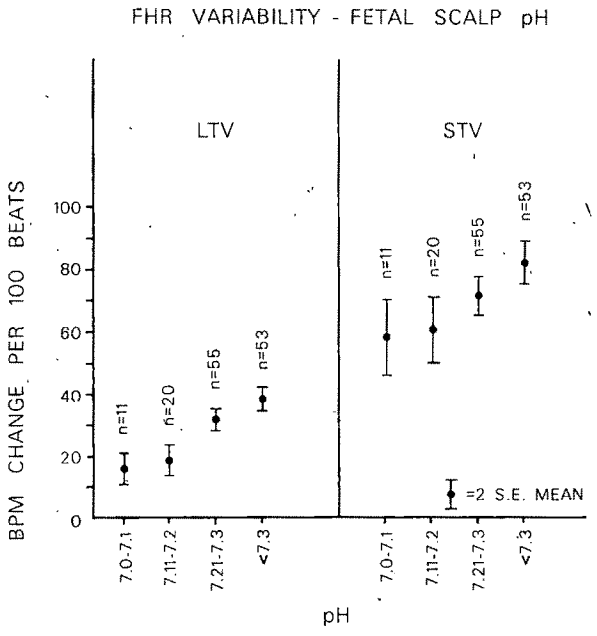


Fig. 4. Significantly increased variability values were found with higher fetal scalp pH values as demonstrated by standard error of the mean comparison.

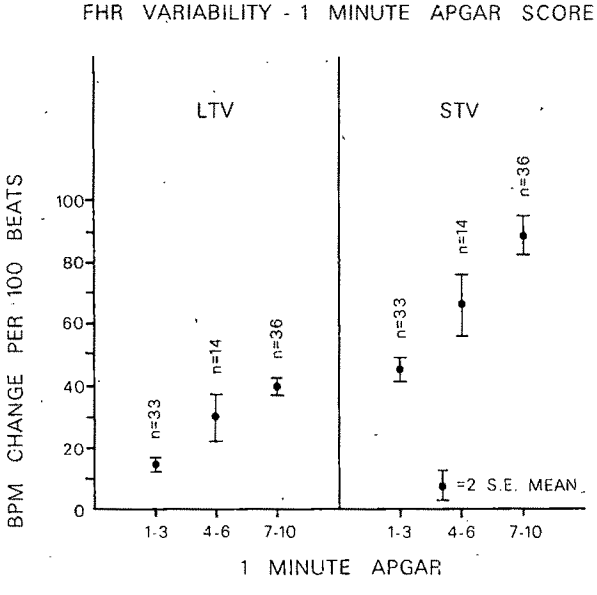


Fig. 5. Baseline variability values the 20 minutes prior to delivery are shown grouped according to the 1-minute Apgar value.

Results

A gradual increase in both long- and short-term variability was seen with advancing labor, both looking at time prior to delivery or at stage of labor relative to cervical dilatation. However, no statistical significance was found in this increasing trend (Fig. 2).

The long- and short-term FHR variability was compared at six stations of the fetal head. There is a gradual increase in FHR variability with descent of the fetal head through the pelvis. The differences found in both long- and short-term FHR variability at −2 station and crowning were statistically significant as shown by comparison of the standard error of the mean (Fig. 3).

Significant differences in both long- and short-term variability were found when fetal scalp pH values of 7.20 or less were compared to higher values (Fig. 4).

When the 20 minutes prior to delivery were evaluated, significant differences were found in both long- and short-term FHR variability in the group of infants exhibiting 1-minute Apgar scores of 6 or less when compared to those with values of 7 or more (Fig. 5).

Comment

The clinical value of variability seems to be well documented, but a detailed numerical study of variability is imprecise because of the effect of FHR variability of factors such as patient movements, vaginal examinations, and maternal medication, as well as artifacts introduced by certain equipment used to record the FHR.

Clinically important is the positive correlation between variability and the condition of the fetus as evaluated by both scalp pH and one-minute Apgar score. The correlations confirm the potential diagnostic and prognostic value of long- and short-term FHR variability as a clinical index of fetal intrapartum condition.

A recognized deficiency of this study was the failure to compare these measures of FHR variability and five-minute Apgar values. It was impossible to subsequently do this comparison because the original data had become unavailable.

This preliminary study suggests that this machine approach of variability assessment is worthwhile. Using this technique, on-line data is currently being collected in both normal and abnormal clinical conditions to further evaluate its potential clinical significance.

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Short-term cycles in human fetal activity

I. Normal pregnancies

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Recordings of fetal motor activity in utero were carried out on 17 women with normal pregnancies at 23 to 37 weeks' gestation. Fetal motility was monitored by a method based on integrative EMG recordings derived through electrodes attached to maternal abdominal surface. Orthogonal spectral analysis revealed 40 minute and 80 minute cycles in fetal motility in 59% of the fetuses. The correlation between objective and subjective (maternal self-assessment) scores of fetal activity was generally confirmed. Methods of monitoring fetal activity, based on short-term recordings, are criticized in the light of the present results. (AM. J. OBSTET. GYNECOL. 134:696, 1979.)

THE INTEREST in fetal motor activity in late pregnancy as an index of fetal health has been recently renewed by the studies of Mathews[1, 2] and Sadovsky and associates.[3, 4] Maternal self-measurement of fetal movements was advocated for high-risk pregnancies as an efficient and reliable monitoring tool.[5, 6]

Nevertheless, despite its utmost simplicity, this test has not gained popularity. It has not been adopted by many obstetricians who prefer to rely on more sophisticated, though expensive, methods of fetal evaluation, involving biochemical and immunologic assays and electronic monitoring.

The general reluctance among obstetricians to rely on maternal self-assessment of fetal movement rate originates in part from the rather empirical knowledge on the existence of periods of "fetal sleep" which are unpredictable and may, therefore, affect the maternal count of fetal movements based on short-term recordings.

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Various methods of continuous fetal movement recording have been described. These included an electromagnetic device,[7] an electrical device based upon the strain-gauge principle,[8] a similar device with piezoelectric material,[9] ultrasound,[10] and a conventional tocodynamometer,[11] set usually to 25 mm Hg, full-scale.[12] In none of the latter was an attempt made to investigate the possible existence of fluctuations in the amount of fetal activity during the recording periods.

Sterman,[13] who utilized pressure-sensitive devices to record fetal activity during maternal sleep, has observed a rhythmic rest-activity cycle ranging in periodicity from 40 to 60 minutes. In a further study Sterman[14] observed the existence of two consistent cycles of fetal activity throughout gestation, with interpeak intervals of 38 and 83 minutes; the latter was associated with maternal sleep REM-NONREM cycles.

The present study was designed to (1) introduce a new, simple, nonintrusive method for recording of fetal activity and (2) re-evaluate the existence and possible clinical significance of short-term cycles in the so-called fetal sleep and wake states and thus, hopefully, lead to improvement and better interpretation of results of the presently recommended methods of monitoring fetal activity.

Methods and materials

Recordings were carried out on 19 outpatients, healthy pregnant volunteers, ranging in age from 17 to 31 years, during gestational periods between 23 and 37

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Table I. Data of 17 normal pregnancies, including details of outcome

Subject	*Age*	*Gravida*	*Gest. age at recording (wk)*	*Gest. age at delivery (wk)*	*Birth weight (kg)*	*Apgar score*	*Fetal sex*
H. T.	21	I	32	40	3,100	9/10	F
S. S.	21	II	37	41	3,350	9/10	M
I. B.	27	II	37	41	4,050	10/10	F
H. G.	21	I	36	40	2,850	10/10	F
Y. S.	24	I	23	38	3,580	9/10	F
I. S.	23	I	30	42	3,500	10/10	M
R. I.	23	I	28	40	3,450	10/10	M
Sh. S.	22	I	30	40	3,700	10/10	F
H. T.	27	I	28	42	3,600	10/10	M
T. R.	28	V	25	40	2,900	10/10	F
R. N.	28	II	28	40	2,600	8/9	F
I. S.	20	I	28	39	3,250	10/10	F
U. K.	22	I	35	41	2,800	10/10	F
K. A.	28	III	35	41	3,250	10/10	M
A. M.	17	I	33	41	2,700		M
S. Sh.	21	I	32	41	3,000	9/10	M
Z. R.	31	II	29	39	2,900	10/10	F

weeks of pregnancy. The study group comprised 17 women who were eventually delivered of normal infants (birth weights, 2,600 to 4,050 grams; Apgar scores, 9 and 10 at 5 minutes) at 39 to 42 weeks' gestation. Thirteen were delivered vaginally and in four a lower segment cesarean section was performed for obstetric indications unrelated to fetal health. All infants experienced normal neonatal periods. Data of individual subjects, including details of pregnancy outcome, are depicted in Table I. Gestational age at the time of recording was retrospectively ascertained through Dubowitz score.

To ensure the recording of unprovoked fetal activity, examination was performed in an isolated, quiet room, with the subject lying comfortably and free to change position. Recordings started following 30 minutes of adaptation, either at 10 A.M., or at 15 P.M., and lasted for 2 to 3 hours. Fetal motility was monitored by integrative EMG recordings (Beckman type 9852A Integrator Coupler derived through electrodes attached to the maternal abdominal surface, with high-frequency cut-off point set at 30 Hz (Beckman type 411R Dynograph). This method enabled the detection of all gross changes of the abdominal surface, which were registered as movement artifacts in the EMG recordings. Four large silver-chloride Beckman type electrodes were taped as in Fig. 1. Additional electrodes were taped on the dorsal surface of the thighs to monitor maternal movements; no integration was used in maternal recordings. Five channels of information were obtained from each woman: bipolar recordings from A to B, D to C, B to D, A to C, and E to F. Recording gains were adjusted to give a low and consistent level of background physiologic activity with a paper speed of 1 mm/second. Since several sources of

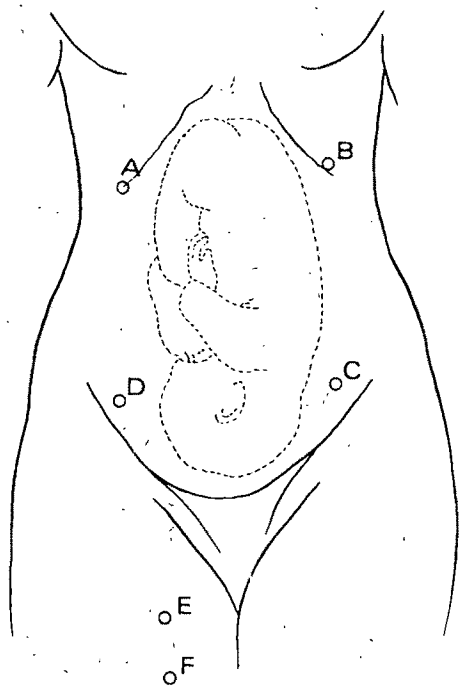


Fig. 1. Schematic illustration showing the position of electrodes attached to maternal abdominal surface (*A, B, C, D*) for recording of fetal movements. Electrodes *E* and *F* monitor maternal movements.

artifactual movements, besides fetal movements, could be induced in the recordings (e.g., subjects' somatic movements, uterine activity, maternal respiratory movements, aortic pulsations transmitted by the uterus to the abdominal wall) a conservative scoring procedure was established. A fetal movement was scored if a movement artifact appeared in all four abdominal

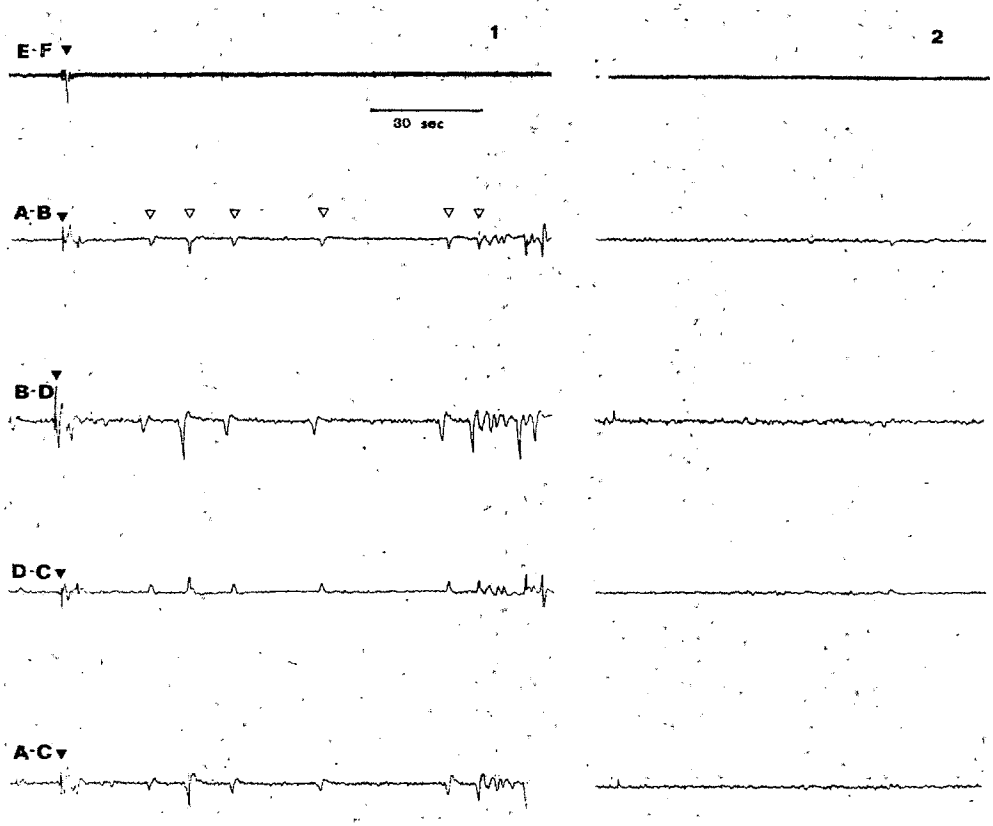


Fig. 2. Example of an original five channel recording of fetal movements. *1,* Phase of activity, characterized by parallel deflections in four channels derived through electrodes attached to maternal abdominal surface (*A-B, B-D, D-C,* and *A-C*). ▽ Fetal somatic movement. ▼ Maternal movement characterized by a concomitant deflection in channel *E-F,* derived through electrodes attached to maternal thigh. *2,* Phase of fetal rest in the same subject. The background physiologic activity is that of maternal abdominal wall.

recording channels without concomitant maternal movement (Fig. 2). Throughout the recordings subjects were under close visual observation and every change in their position was noted on the polygraphic paper. Subjects were awake throughout most of the recording sessions.

To test the validity of the recordings, five subjects were provided with a microswitch connected to a sixth polygraphic channel and were requested to press it whenever they felt a fetal movement. Pearson product moment correlation coefficients were then calculated between the subjective and objective motility scores.

Time series construction. Since we a priori hypothesized the existence of short-term periodicity in fetal motility, time series were constructed from the activity scores. These were obtained in the following way: Recordings were cut into 5 minute segments which were coded and then randomly ordered. Each 5 minute segment was subdivided into 30 second intervals, and the number of 30 second intervals containing at least one fetal movement was determined for every segment. Hence, the score of fetal activity ranged from 0, when no movements occurred in a 5 minute segment, to 10, when movements occurred in every 30 second interval. Finally, time series were constructed by reordering the fetal activity scores according to their chronological order.

Statistical analysis. To determine the rhythmic structure of the data an objective statistical procedure, orthogonal spectral analysis,[15] was employed. In this technique, the data are correlated with a set of trigonometric functions with known periodicities, and the trigonometric function with the best correlated periodicity is determined. The number of periodicities that can be correlated with the data, i.e., the resolution of the spectra, is limited by the total length of the recording and the length of the sampling interval.

Results

Fetal movements were easily detected by this method, and could be clearly differentiated from maternal movements or background respiratory activity. Pear-

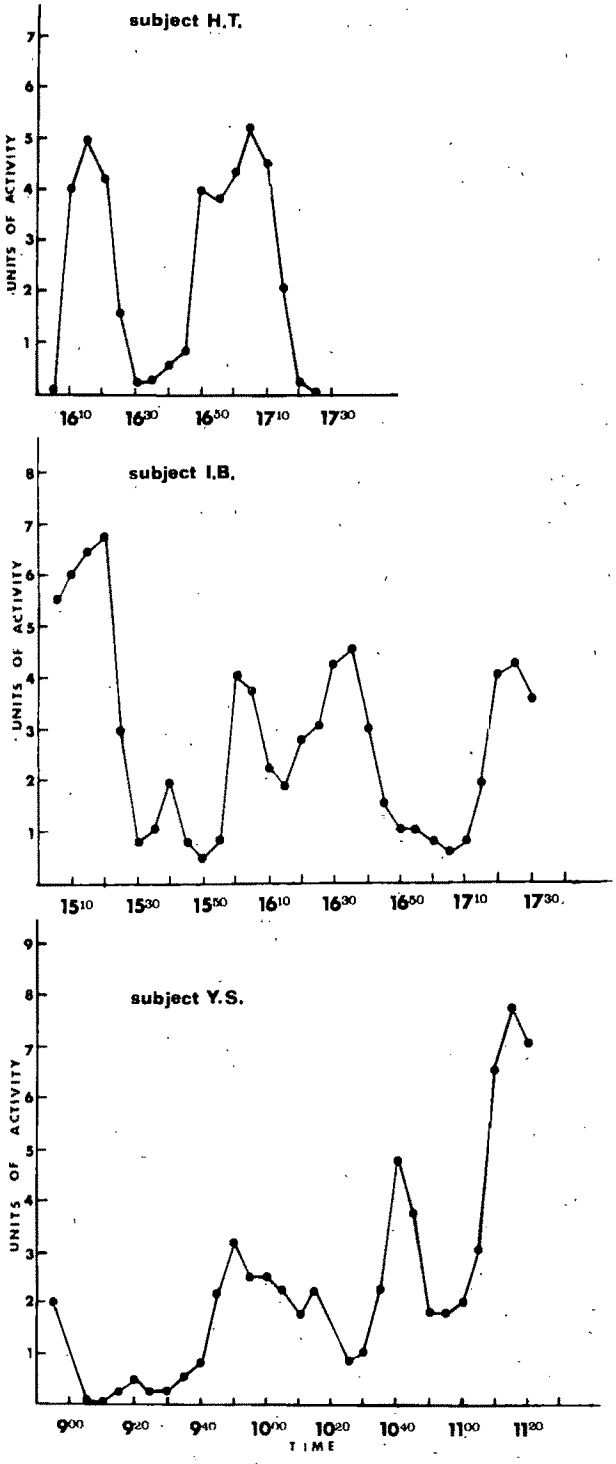


Fig. 3. Three examples of periodicities in fetal activity at different gestational ages, all within the range of 40 to 80 minutes/cycle. This pattern has been revealed by spectral analysis of the fetal movement recordings. *Time* indicates hour of recording. *Units of activity* implies a score of fetal activity ranging from 0, when no movements occurred in 5 minute segment, to 10, when movements occurred in every 30 second interval of fetal movement tracings (see text). Time series were smoothed by three point moving average procedure.

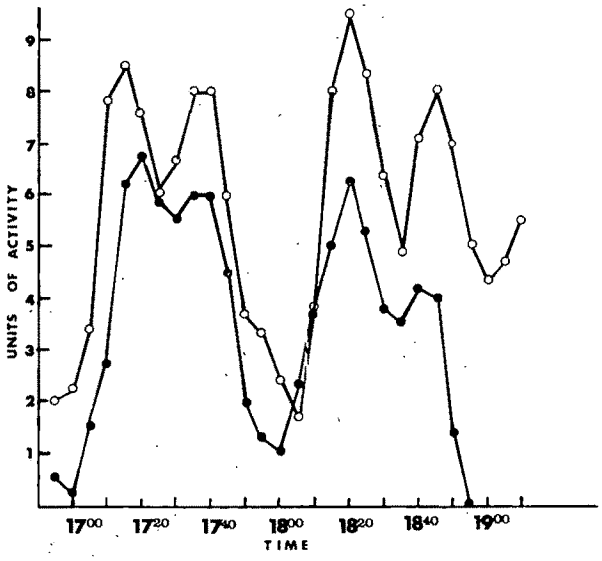


Fig. 4. Correlations between objective (empty circles) and subjective (filled circles) scores of fetal activity in a late normal pregnancy (Subject R. I., Table I). Note the accordance of periodicity, albeit the total number of maternally counted movements is consistently somewhat lower than those recorded through abdominal surface.

son product moment correlations between the objective and subjective scores of fetal activity in five cases were: 0.573 ($p < 0.001$), 0.68 ($p < 0.001$), 0.56 ($p < 0.001$), 0.364 ($p < 0.05$), and − 0.18. (Subjective scores of fetal activity were obtained in a way similar to that of the objective scores; that is, in each 5 minute segment the number of 30 second intervals with at least one movement was determined.)

Fig. 3 presents examples of three time series constructed from objective fetal activity scores. Cycles of motility are visible in all records. The mean interpeak interval was 45 minutes (SD = 7.68), well within the range of periodicities previously reported.[13, 14] Fig. 4 presents objective and subjective recordings; the similarity between the records is obvious.

Spectral analysis was calculated from the autocorrelation functions for eight spectral frequencies. Spectra were individually hanned (smoothed) and normalized to yield spectral density functions. Six subjects (35%) had the highest spectral peak at the frequency 36 cycles/day, corresponding to a periodicity of approximately 40 minutes/cycle, and four subjects (24%) had the highest spectral peak at the frequency 18 cycles/day, corresponding to a periodicity of approximately 80 minutes/cycle. The other seven subjects (41%) had the highest spectral peak at the zero frequency, which indicated either a dominant linear trend or frequencies much slower than 18 cycles/day. Three-hour recordings were too short for differentiation between

these possibilities in individual cases. The mere existence or nonexistence of short-term cyclicity in fetal activity was found to be correlated neither to gestational age at the time of recording, nor to fetal sex, birthweight, and Apgar score.

Thus, in more than 50% of the subjects spectral analysis revealed periodicities within the range of 40 to 80 minutes/cycle. Due to the limitations of the statistical technique because of the short recording periods, the range of 40 to 80 minutes/cycle is somewhat larger than the range of 40 to 60 minutes/cycle reported earlier. It seems, nevertheless, close enough to suggest the existence of short-term periodicity in fetal activity, which operates during maternal sleep and waking.

Comment

The renewed interest in fetal activity recording as a test for fetal well being has stimulated many investigators in the field of fetal monitoring. Thus, attempts were recently made to characterize various forms of fetal activity,[12] to develop a reliable device for the objective recording of fetal movements,[8, 9] and to establish the correlation between the objective (electronic) and subjective (maternal self-assessment) modes of fetal activity determination.[7, 16] Goodlin and Lowe[16] have noted a diurnal variation in fetal movements with a peak of fetal activity at around 1800 to 2100 hours. Increased fetal activity in the evening has also been noticed by Spellacy and associates[17] as well as by Wood and associates,[8] who have also observed, in some patients, the occurrence of daily and weekly variations in fetal movements.

The existence of short-term periodicity in fetal activity has been suggested by Sterman,[13, 14] but he was concerned mainly with the possible correlation between maternal sleep and fetal motor activity. Our findings confirm the existence in late normal pregnancy of a rhythmic rest-activity cycle at the range of 40 to 80 minutes/cycle which is not limited to maternal sleep. This phenomenon has been totally ignored by investigators who attempted to evaluate the correlation between fetal activity and fetal well being. This could have led to inaccuracies in fetal activity estimation. Thus it could have accounted for the sporadic daily variation that was observed in some patients by Wood and associates.[8] The 20 minute periods of maternal self-recording as recommended by these authors appear to be about half the shortest of fetal rest-activity cycles. Thus, any randomly selected period of 20 minutes can easily fall within a resting phase. Sadovsky and Polishuk[6] have suggested that whenever the estimated number of movements is less than three per day (as calculated from three self-recording periods of 30 to 60 minutes duration), the recording should be continued for 6 to 12 hours per day. By this means the difficulty raised by the short-term periodicity is virtually overcome. However, as pointed out by Wood and associates,[8] which is in agreement with our experience, patients find it difficult to concentrate on long-term self-recording, rendering their records unreliable. This is especially true in patients with high-risk pregnancies with high anxiety levels.

By 2 to 3 hour periods of recording we have confirmed the correlation between objective and subjective scores of fetal activity in four out of five patients with normal pregnancies. The lack of correlation in the fifth case demonstrates, as previously noted,[8] the variable reliability of patients as observers. In this particular case it could be due to lack of attention on the part of the subject, who had difficulties following the unusually large number of movements that occurred in this recording.

The need for a simple and reliable recording device of fetal movements is obvious. The method of maternal abdominal EMG recording, as described in this study, is nonintrusive to the fetus and is highly reliable by easy elimination of artifacts. Its clinical applicability remains questionable, and merits further investigation, yet, it seems promising and is of definite value as a tool in the research of fetal motor activity.

A longitudinal study throughout the third trimester of pregnancy may help clarify the possible existence of a changing trend in the time relations between active and resting phases of fetal behavior in utero. Such a trend could be anticipated in the light of available data on wake and sleep states in premature infants.[18]

We thank those women attending the prenatal clinic of Rothschild University Hospital who kindly consented to participate in this study. We are also grateful to the staff of our neonatal department for meticulous examination of the neonates.

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The value of lecithin/sphingomyelin ratios in diabetes: A critical review

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The value of the lecithin/sphingomyelin (L/S) ratio in the management of high-risk pregnancies has been widely accepted. A group for which major controversy still exists is the pregnancy complicated by diabetes mellitus. Some studies, such as our own, report great success with the use of the test in this disorder, while others have been unable to rely upon it. This problem prompted a closer look at our own data, with a specific analysis of the factors which may explain the discrepancies. Specifically, a subgroup of our population was selected by limiting the study to 93 patients in White Classes B through R whose L/S ratio determinations were 2.0 or above within three days of delivery. A comparison was made of this group of patients with those of the most recent conflicting report, that of Mueller-Heubach and co-workers[8] at the Magee-Women's Hospital in Pittsburgh. The study populations appeared similar in the distribution of disease severity and gestational ages of those patients with L/S ratios over 2.0. The incidence of respiratory distress syndrome (RDS) in those infants with L/S ratios over 2.0 was compared. The group in Pittsburgh reported an 18% incidence, while we have observed a 5% incidence in this population. The factors which may explain this difference include the definition of RDS, the inclusion of Class A patients in a series, and methodologic differences in the preparation of specimens for the determination of the L/S ratio. None of these factors can conclusively explain the disparity in these studies. However, when taken together they do appear to offer a plausible explanation for such differences. It appears essential to standardize both laboratory procedures and criteria for evaluation of neonatal outcome before comparing results. (AM. J. OBSTET. GYNECOL. 134:702, 1979.)

THE CONTRIBUTION made to the management of high-risk pregnancies by the lecithin/sphingomyelin (L/S) ratio cannot be overstated. Respiratory distress syndrome (RDS) due to iatrogenic premature delivery is no longer an everyday concern. One area where this has not been clearly resolved appears to be that of the diabetic pregnancy.

Although many reports in the past indicate that the L//S ratio is just as reliable in diabetic as in other pregnancies,[1–4] some have claimed that it has led them astray.[5–8] Several articles have appeared within months of each other with conflicting results.

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Dahlenburg and associates[5] in Melbourne noted a 27% incidence of mild or moderate RDS with an L/S ratio of 2.0 or greater in their diabetic patient population. They seriously questioned whether or not the risk of amniocentesis is justified in this group.

Mueller-Heubach and coworkers[8] have reviewed 101 diabetic pregnancies, primarily White[9] Classes B through D, delivered between 34 and 41 weeks gestation. They report an 18% incidence of RDS among 54 infants with L/S ratios of 2.0 or greater. Fifty-nine percent of these infants were delivered by cesarean section and had a 28% incidence of RDS. RDS occurred in 4.5% of babies with a mature L/S ratio who were delivered vaginally.

Our report a few months earlier[3] reviewed 210 diabetic pregnancies, Classes B through R. Two hundred L/S ratios were 2.0 or higher. We noted a 3% incidence of RDS in this group, which was not different from the 2.6% noted in our general population.[10] This disparity in results prompted the following evaluation of our data.

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Patients and procedures

For this study, our examination was limited to those diabetic women who were delivered within three days of determination of the L/S ratio. Only those patients with an L/S ratio of 2.0 or greater were accepted, and those whose fluid was contaminated with blood or meconium were also excluded. All patients were managed at Women's Hospital, Los Angeles County–University of Southern California Medical Center.

The study group consisted of 93 patients delivered between 1970 and 1977. The original study concluded in June, 1976, but additional patients meeting these criteria in the following year were accepted for study. The breakdown by White classification was as follows: 63 Class B, 16 Class C, 10 Class D, 3 Class F, and 1 Class R. The distribution by weeks of gestation completed is shown in Table I.

All amniotic fluid specimens were spun for ten minutes at 2,200 rpm, which corresponds to 1,660 × g. The L/S ratios were determined by the method of Gluck with the Borer modification and the planimetric method.

Results

In the Los Angeles County–Women's Hospital series, the incidence of RDS remained 5.4%. The individual cases are shown in Table II. RDS occurred in 3/20 cases with an L/S ratio between 2.0 and 2.49, 1/27 between 2.50 and 2.99, 1/15 between 3.0 and 3.49, and 0/31 with a value of 3.5 or above. When analyzed by route of delivery, there were four cases of RDS in 56 patients delivered by cesarean section, for an incidence of 7.1%, and one case in 37 patients who had a vaginal delivery, for a 2.7% incidence. These numbers are too small for statistical tests of significance.

Comment

Our data continue to show that the reliability of the L/S ratio is no different in the woman with diabetes than in the nondiabetic patient. Why then does the same test run on an equivalent population in Pittsburgh give markedly different results? Possible explanations include a statistical accident, different patient populations, lack of consistency in neonatal diagnosis, or alterations in methods of L/S analysis. We will now examine these possibilities.

The statistical problem can be addressed easily. The chance of our finding five cases of RDS out of 93 patients, while another group finds 23 out of 101 cases, when both come from the same basic population, yields a chi square value of 10.49. Thus this would occur by chance with $p = 0.0012$, or once in a thousand times.

Table I. Distribution of gestational ages in the study population

	Weeks' gestation at delivery							
	34	*35*	*36*	*37*	*38*	*39*	*40*	*41*
No. of patients	6	7	14	12	32	11	8	3

Table II. Deliveries associated with RDS in diabetic pregnancies with L/S ratios of 2.0 or above obtained within 72 hours of delivery

Class	*Weeks' gestation*	*L/S ratio*	*Route of delivery*
B	38	2.1	Cesarean
B	35	2.3	Cesarean
D	35	2.4	Cesarean
B	36	2.8	Vaginal
B	38	3.3	Cesarean

Do the patient populations differ? Gluck and associates[11] have reported that Class A diabetes is characterized by a delay in pulmonary maturation as reflected in the L/S ratio. These patients have been excluded from our series. We do not use the L/S ratio in their management, and only rarely resort to early intervention in this group.[12] The magnitude of this problem is difficult to evaluate, as the report by Mueller-Heubach does not give the number of Class A patients with L/S ratios over 2.0. There were at least six patients with values of less than 2.0, and two cases of RDS with values of 2.0 or above. If one excludes the six immature cases, one is left with a maximum of 13 Class A patients with L/S ratios over 2.0, and two cases of RDS. The remaining group then comprises 14 cases of RDS in 70 patients, or a 20% incidence. This analysis implies that the Class A group has not contributed an excessive amount to the incidence of RDS.

The mean gestational age at delivery in our present series from Los Angeles County-Women's Hospital is 37.5 weeks, while the subpopulation in the Mueller-Heubach series with L/S ratios greater than 2.0 appears to have a mean age of 37.2 weeks.* These figures are certainly comparable.

The next area to consider is the diagnosis of RDS itself. It is probable that all of the cases described by Mueller-Heubach have RDS, but when reporting on this condition, it would be preferable to specifically state the radiologic criteria used for the diagnosis. This is important as transient tachypnea of the newborn infant, sepsis, and some congenital heart lesions can pre-

*Data derived from their graphs and tables.

sent with identical clinical pictures. Definitive diagnosis is essential.

The final problem which remains is the methodology of the test itself. Since the original publication of Gluck's work, there have been scores of different approaches to the determination of the L/S ratio or measurement of surfactant. Two of the most crucial differences in L/S ratio techniques may be the inclusion or exclusion of the acetone precipitation step (used by both papers discussed here), and the use of the planimetric method as opposed to the densitometric method of measurement. Our laboratory has used the planimetric method, which may lead to a false elevation of the ratio.[13] This should give us a higher incidence of unsuspected RDS than a laboratory using a densitometer. The report from Pittsburgh involved the use of both methods, which may add some variability to their results.

Recently, Cherayil and colleagues[14] reported yet another source for nonreproducibility of the L/S ratio. They discovered that the g-force used in centrifugation can have a major effect upon the L/S ratio found in amniotic fluid. The method used at Los Angeles County-Women's Hospital falls in the steepest portion of their curve. This is apparently enough force to change a fluid with a L/S ratio of 2.6 when unspun to a value of less than 2.0 after centrifugation. The report from Pittsburgh suggests that fluid was not centrifuged if the determination was done immediately. This technique could lead to values which are misleadingly high.

When taken individually, it is difficult to say that any one of these differences has led to our conflicting results. When taken together, however, it would seem reasonable to conclude that they do explain the discrepancies. Specifically, an L/S ratio of 2.0 or above, done in our laboratory on spun fluid from an overtly diabetic patient, appears to provide assurance that that infant will not develop RDS any more often than a nondiabetic infant in the same circumstance. Before any further claim to the contrary is made, it seems essential that we agree upon our methodology, terminology, and study populations.

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Performance of the amniotic fluid foam stability–50 percent test

A bedside precedure for the prenatal detection of hyaline membrane disease

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A study was conducted on 394 patients in order to evaluate a modified foam stability (FS) test for the prenatal evaluation of fetal pulmonary maturity. We termed the assay the "FS-50 test" because of its dependence upon the maintenance of a 50% ethanol concentration in the final assay mixture. The FS-50 test was regarded as "positive" when an uninterrupted ring of stable bubbles formed around the meniscus of the tube at the air-fluid interface, following vigorous shaking. Anything less was regarded as a "negative" result. Neonatal hyaline membrane disease (HMD) did not occur in association with a "positive" FS-50 test result. However, when the FS-50 test was "negative," 35.8% of the neonates developed HMD. In 164 of the 394 patients studied, sufficient amniotic fluid was available so as to enable us to perform the FS-50 and the lecithin/sphingomyelin (L/S) ratio assay concurrently. L/S ratio values of greater than 2.0 correctly predicted a sufficient degree of fetal pulmonary maturity so as to protect against the subsequent development of HMD in 97.8% of the cases. L/S ratio values of less than 2.0 were predictive of HMD in 28.4% of the cases studied, while a "negative" FS-50 test correctly predicted that HMD would subsequently occur in 46.9% of the cases. The FS-50 test promises to provide a reliable screening method for the prenatal detection of HMD. The practicability and sensitivity of this simple assay makes it a potentially valuable addition to our diagnostic armamentarium. (AM. J. OBSTET. GYNECOL. 134:705, 1979.)

THE IDEAL prenatal test of fetal pulmonary maturity should be simple, sensitive, accurate, and inexpensive. At present, the two most widely used methods of predicting fetal pulmonary maturation are the lecithin/sphingomyelin (L/S) ratio[1] and foam stability tests.[2–4] The L/S ratio has been found to be reliable in normal obstetric cases but has shown less predictive value in complicated situations.[5–7] The assay is time consuming, requires sophisticated equipment and technical expertise, and in most laboratories cannot be performed on a stat basis.

We recently reported on a preliminary evaluation of a modified amniotic fluid, foam stability test for the prenatal detection of neonatal hyaline membrane disease (HMD).[4] The assay is a modification of a procedure first described by Clements and colleagues[2] in 1972. We termed the assay the FS-50 test because it makes use of 100% ethanol in a 1:1 ratio with uncentrifuged amniotic fluid to produce an ethanol volume fraction of 50% in the final assay mixture. This distinguishes it from the procedure originally described by Clements' group in which the final ethanol volume fraction in the assay mixture was 47.5%. We were able to demonstrate that a positive result using the FS-50

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Table I. Clinical presentations of the 394 patients

Clinical presentations	*No. of cases*
Normal pregnancy (including elective cesarean sections)	160
Hypertension (toxemic and nontoxemic)	94
Preterm delivery	83
Diabetes mellitus (insulin-dependent)	47
Intrauterine growth retardation	20
Rhesus disease	17
Third trimester bleeding	12
Chronic renal disease	5
Total	438

Table II. FS-50 test versus clinical outcome

	Neonatal pulmonary status	
FS-50 test	*Normal*	*HMD*
+	285	0
−	70	39

Table III. L/S ratio and FS-50 results versus incidence of HMD

	L/S ratio					
FS-50 test	*<1.0*	*1.1-1.5*	*1.6-2.0*	*2.1-3.0*	*>3.0*	*Total*
+	0/1*	0/7	0/27	0/38	0/42	0/115
−	8/10	12/17	1/12	2/9	0/1	23/49
Total	8/11	12/24	1/39	2/47	0/43	23/164

$$*\text{Key} = \frac{\text{Cases of HMD}}{\text{Total cases}}$$

Table IV. Predictive values of L/S ratios and of FS-50 test results

Conditional probability	*Based on 164 cases (%)*	*Based on 394 cases (%)*
P(Normal | L/S > 2.0)	97.8	—
P(HMD | L/S ≤ 2.0)	28.4	—
P(Normal | FS-50 plus)	100	100
P(HMD | FS-50 minus)	46.9	35.8

test provided 100% assurance of protection against the subsequent development of HMD in the neonatal period.[1]

While the results of our preliminary study were extremely encouraging, the sample size was relatively small (i.e., only eight cases of HMD in a total of 104 patients studied) and the assay was performed under optimal conditions by a laboratory-trained technologist.[3] This present study presents an evaluation of the FS-50 test under routine clinical conditions with the assay being performed by a number of clinicians as a bedside procedure. In addition, the sample size is now much larger (i.e., 39 cases of HMD in a total of 394 patients studied).

Patients and methods

This study represents a collaborative undertaking between the North Carolina Memorial Hospital in Chapel Hill and the Charlotte Memorial Hospital in Charlotte; both are institutions affiliated with the University of North Carolina School of Medicine. Amniotic fluid was obtained by amniocentesis performed for clinical reasons and done within 48 hours of delivery in all cases. Fluid found to be macroscopically contaminated with blood or meconium was discarded.

Table I presents the demographic characteristics of the 394 patients studied. The majority of patients had complicated gestations. Pulmonary status of the neonate was defined as either "hyaline membrane disease" or "normal" on the basis of criteria previously defined in our earlier publication.[4]

We performed the FS-50 test on each of the amniotic fluid specimens obtained from the 394 patients included in the study. Both institutions had at their disposal previously provided Kimax glass tubes measuring 5 cm × 1.3 cm, each of which contained exactly 1.0 ml of 100% (absolute) ethanol which had been dispensed into the tubes in a moisture-free environment. All tubes were sealed with an air-tight, screw-on cap. This procedure insured maintenance of the anhydrous nature of the absolute ethanol reagent. The procedure of the FS-50 test was performed as follows: One milliliter of freshly obtained amniotic fluid was dispensed into a glass tube containing 1.0 ml of ethanol. The tube was recapped and then vigorously shaken for a period of 30 seconds. It was then allowed to settle for 15 seconds after which the air-fluid interface was examined for the absence or presence of stable foam. The presence of an uninterrupted ring of bubbles around the entire meniscus of the tube was interpreted as "positive" and anything less was called "negative".[4]

In 164 of the 394 patients studied, the lecithin/sphingomyelin (L/S) ratio was also performed on the same specimen of amniotic fluid. The L/S ratio was performed according to the method described by Gluck and associates[1] and included the acetone precipitation step.

Results

Table II compares the results obtained with the FS-50 test versus neonatal clinical outcome. The incidence of hyaline membrane disease was 11%. In no instance did hyaline membrane disease occur in association with a "positive" FS-50 test. HMD occurred in

39 of 109 cases where the FS-50 test was "negative" (i.e., 35.8%).

Table III depicts the results obtained on each of the 164 cases where both the L/S ratio and FS-50 test were performed on the same specimen. In this subset, the incidence of hyaline membrane disease was approximately 14% (i.e., 23 cases of hyaline membrane disease out of a total of 164 patients studied). Two cases of hyaline membrane disease occurred in association with L/S ratio values of greater than 2.0, i.e., 2.5 and 2.8, respectively. In both instances, delivery was achieved by elective cesarean section. One- and five-minute Apgar scores were greater than 7.0 in both cases. In the case associated with the L/S ratio of 2.5, pregnancy was complicated by the nephrotic syndrome and hypertension while the case associated with an L/S ratio of 2.8 was a patient in preterm labor who had had a previous cesarean delivery.

Table IV presents the predictive values of the L/S ratios as compared to the FS-50 test results, based upon the data presented in Tables II and III. We selected a cutoff value of 2.0 for the L/S ratio which is generally accepted as the value above which neonatal HMD will not occur. Using this cutoff value for the L/S ratio, we note a 97.8% predictive reliability for results of greater than 2.0 and 28.4% for values below 2.0. For the FS-50 test, we note that when a "positive" result was assumed to indicate that neonatal HMD will not occur, the predictive reliability was 100%. A "negative" FS-50 result, on the other hand, correctly predicted that HMD would occur in 46.9% of the 164 cases.

Comment

Hyaline membrane disease is one of the major causes of perinatal death throughout the world. In the United States alone it is responsible for approximately 25,000 deaths and numerous serious sequelae each year. The major method for the prenatal detection of this disease is the L/S ratio which is employed to measure surfactant in the amniotic fluid. Unfortunately, however, this assay is expensive and requires the availability of a significant amount of technical expertise. In Addition, it is time consuming and therefore is not readily available on a 24 hour stat basis. Moreover, we as well as other workers have noted hyaline membrane disease in association with L/S ratio values of greater than 2.0, especially in pregnancies complicated by diabetes mellitus and Rhesus disease.[4, 5–7] In addition, this study revealed that when L/S ratio values were less than 2.0, 71.6% of the neonates had mature lungs, as compared with 53.1% when the FS-50 test was "negative."

The FS-50 test as described here, by providing prefilled glass tubes containing the required amounts of absolute ethanol, significantly simplifies the shake test procedure, thereby reducing the likelihood of variation in the final ethanol volume fraction. We are convinced that it is this factor more than any other which has avoided the occurrence of "false positive" results in our study. All that is required of the analyst (e.g., the clinician doing the assay) is the ability to pipette the prescribed volume of amniotic fluid and then to shake the assay mixture for 30 seconds. While the results would suggest that the FS-50 test provides a reliable screening method for hyaline membrane disease, final clinical acceptance of this assay must await the outcome of a more extensive study.

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Collection and use of autologous fetal blood

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A prospective study was completed to evaluate the feasibility of autologous fetal blood collection. Following puncture on the umbilical vein, fetal blood was drawn into sterile heparinized plastic syringes and aliquots were subjected to coagulation and culture studies. None of the blood samples exhibited significant growth of bacterial pathogens and all patients had normal coagulation studies at 24 hours of age. These data demonstrate that fetal blood can be safely collected and given to infants subjected to shock or iatrogenic blood loss. (AM. J. OBSTET. GYNECOL. 134:708, 1979.)

PRETERM INFANTS may exhibit hypotension following hemorrhage or iatrogenic blood loss. The mortality rate in these infants is higher than 50%.[1, 2] Current blood-banking techniques do not provide autologous blood, and heterologous blood for emergency transfusion is not always readily available. We have completed the following study to evaluate the safety of one method of collecting autologous fetal blood.

Material and methods

Patient population. This study was the predecessor of a two-year clinical investigation designed to evaluate the efficacy of fluid therapy for neonatal shock. Thus, all blood withdrawn and infused into the infants described herein was used with full consent of the parents and approval of the University's Human Protection Committee.

The author was present in the delivery room for collection of fetal blood from each of the infants in the study. In each instance, an attempt to withdraw fetal blood from the umbilical cord–placental unit was made. The infants in shock received initial empiric therapy of 25 ml/kg body weight, and the other infants received 10 ml intravenous aliquots of autologous blood to replace volume loss on a milliliter-per-milliliter bases.

All infants had venipuncture samples drawn for completion of coagulation studies before and after transfusion, and at 4 and 24 hours. Blood cultures were completed on each sample withdrawn.

Fetal blood collection. Prior to delivery of the placenta, umbilical cords were doubly clamped and the infants were removed. After each infant has been separated from its clamped cord, fetal blood was obtained from the umbilical cord–placental vascular compartment by an adaptation of the federal regulations for heparin collection of human blood products.[3] A sterile heparin solution (aqueous United States Pharmacopeia grade porcine intestine heparin, Abbott Labs.) was diluted with sodium chloride to prepare a final solution containing 320 units of heparin per milliliter of solution. Thirty-five-milliliter plastic syringes were fitted with 18 gauge needles and then aseptically "primed" with heparin by aspiration of 0.5 ml of the final heparin solution into the syringes. All syringes were prepared daily under laminar flow conditions.

Seventy milliliters of blood was drawn into the two heparin "primed" syringes following a single needle puncture of the umbilical vein. The umbilical cord was washed with Betadine and rinsed with sterile saline prior to venipuncture. Ten milliliters of blood from the second syringe was separated into aliquots for aerobic and anaerobic bacterial cultures and for coagulation studies. The remaining blood (approximately 60 ml) was filtered through a microaggregate administration set just prior to infusion using a high-capacity 10 μ transfusion filter as shown in the diagram (Fig. 1).

After the blood was filtered, it was used as dictated by each infant's blood pressure or by the volume of iatrogenic blood sampling. The blood was suspended at each infant's Isolette until each infant was four hours of age. For the infants in shock most of the blood was used in the initial transfusion. For the other infants, the blood packet was used a second time in 48 instances. If

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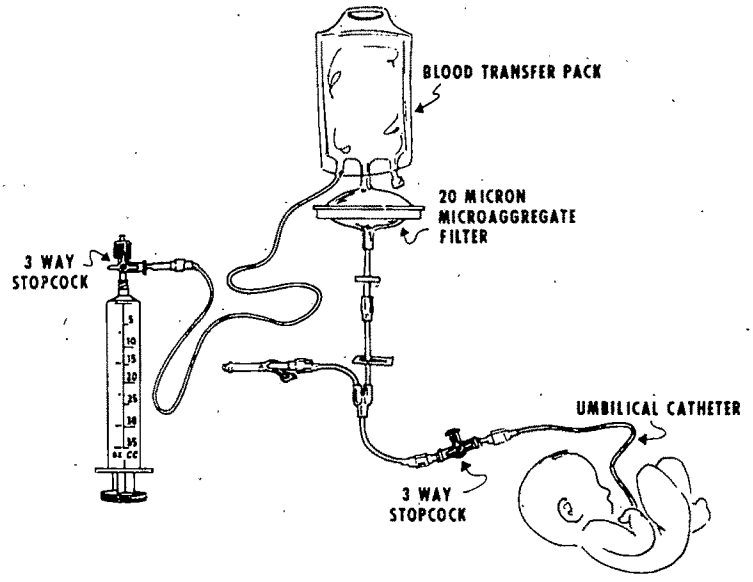


Fig. 1. Diagram of fetal blood administration apparatus.

the infant was not hypotensive, or in need of volume replacement by four hours of age, the blood was refrigerated. No packet was sampled a third time, and no fetal blood more than 12 hours old was used.

Fetal blood testing. Samples of 1 ml. of fetal blood were placed into peptone transfer broth tubes and then plated onto chocolate agar, defibrinated sheep blood agar, and Brewer thioglycollate agar for aerobic and anaerobic cultures. All samples were grossly and microscopically examined at 1, 2, and 7 days.

Samples of 4½ ml of fetal blood were placed into tubes containing 0.5 ml of 3.8% sodium citrate. Samples were centrifuged and plasma removed and tested within 1 hour. All specimens for coagulation were tested in duplicate by fibrometer techniques previously reported for partial thromboplastin times (PTTs).[4]

Results

Patient population. Twenty-five of the infants in shock survived. Demographic factors and each infant's pressure response will be described elsewhere.[2] None of the patients who received blood transfusions to prevent iatrogenic hypovolemia demonstrated hypotension by 4 hours of age. Without these immediate transfusions, several could have become hypotensive from iatrogenic hypovolemia.

Coagulation studies on the peripheral blood samples demonstrated prolonged PTTs in more than half of the patients who were in shock. However, by 24 hours of age, all patients had normal PTT values (±10% of control values). None of the blood samples obtained prior to or following fetal blood transfusion demonstrated significant anaerobic bacterial growth. Only a single aerobic culture obtained following the second transfusion to one infant grew out diptheroid organisms. The infant survived and never exhibited clinical signs of infection.

Fetal blood collection and testing. On three occasions, difficulty in collection of fetal blood was encountered and only 6, 20, and 25 ml were obtained. In all other instances, a single venipuncture produced a free flow of blood and uncomplicated collection of 35 ml of blood or more. Of the blood placed into the filtration apparatus, approximately 10 ml was "lost." Nearly 50 ml of blood was available for transfusion to each patient. Coagulation tests demonstrated adequate anticoagulation of all fetal blood samples prior to infusion (PTT > 180 seconds). None of the fetal blood samples demonstrated significant bacterial growth at any of the time intervals examined.

Comment

The most optimum technique for supplying fresh blood for the ill human newborn infant is a controversial subject. The two techniques most commonly employed are the use of "walking blood donors" and banked adult whole blood.[5]

Those physicians who argue in favor of the use of "banked blood" state that the "walking donor" system is not a "controlled, safe" technique. Those physicians who favor the "walking-donor" systems argue that this procedure reduces the risk of infectious hepatitis and the lag time from need of blood until transfusion. In our experience, the major advantage of the "walking-

donor" system is its ready availability, but this is often impractical because each infant's donor may be at home, and a long delay from time of need to time of transfusion occurs. Furthermore, the lower hematocrit of the healthy human adult makes it necessary to prepare partially packed red blood cells to provide a "whole blood" transfusion with normal neonatal hematocrit of 55 to 60%. Banked citrated whole blood carries similar disadvantages and it too must be processed to a higher hematocrit before transfusion.

The major advantages of using fetal blood are its immediate availability and its autologous nature. Neither of the other two techniques can provide "compatible" blood immediately at the time of delivery. Neither technique can offer the newborn patient fresh whole blood with no potential risk from foreign erythrocytic, leukocytic, platelet, or protein antigens. A preliminary report has suggested that transfusion of adult heterologous blood to preterm babies may increase the risk of retrolental fibroplasia.[6] Although this potential risk requires further documentation, use of autologous fetal blood allows avoidance of this problem.

No medical therapy is without some potential risk. The problems which could result from use of heparinized autologous fetal blood are the problems of infection, hyperbilirubinemia, or excessive heparinization. Because none of the fetal blood samples revealed significant bacterial growth after 7 days of culture, we conclude that our method of collection following sterile delivery is safe.

Theoretically, hyperbilirubinemia could result from heparin-induced displacement of bilirubin from albumin.[7] It is difficult to evaluate this potential problem in human infants; however, only one of these patients required an exchange transfusion for hyperbilirubinemia (indirect bilirubin > 15 mg/dl).

The possibility of excessive heparinization in patients treated with heparinized blood is one concern partially substantiated by the prolonged PTT studies in our patients treated for shock. However, normal coagulation studies in all of the infants by the end of the first day suggest that heparinization was minimal. Furthermore, comparison of our survival rate for patients in shock with those rates previously reported (86% versus 50%) demonstrates that the benefit of transfusion is well worth the risk of excessive heparinization.

This study suggests that fetal blood may be safely collected and used up to 12 hours following delivery of the ill human newborn infant. To date, we have observed no detrimental effects of use of heparinized autologous fetal blood.

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The effects of prolactin on pulmonary maturation in the fetal rabbit

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The effect of ovine prolactin administration on the fetal rabbit pulmonary pressure volume relationship was determined. Using pentobarbital anesthesia, on Day 24 of gestation, a midline incision on the maternal abdomen was made to expose the bicornuate uterus. Fetal rabbits in one horn of the uterus were injected intramuscularly with a dose of 1.0 mg (0.05 ml) of prolactin solution. Similarly, fetuses in the opposite horn were administered an equivalent volume of control vehicle. On Day 26 of gestation, no significant enhancement of lung maturation, as judged from the pressure volume relationship, was found to result from prolactin administration. These results suggest that prolactin does not initiate the secretion of surface active material into the alveolar lumen of the fetal lung in sufficient amounts to induce physiologic maturation of the rabbit fetal lung. (AM. J. OBSTET. GYNECOL. 134:711, 1979.)

RESPIRATORY distress syndrome, characteristic of premature infants,[1] has been found to be the clinical consequence of high surface tension at the alveolar air-tissue interface.[2] This results in the collapse of the alveoli at low transpulmonary pressures, that is, during expiration. The abnormally high surface tension is the result of a low concentration of pulmonary surfactant lining the alveoli.[3, 4] Normally, the presence of surfactant reduces surface tension at the air-tissue interface and thus prevents collapse of the alveoli at low pressures.[5, 6] Current evidence suggests that most of the surface active material present in the lung is synthesized, stored, and secreted by type II alveolar pneumocytes.[7] This sequence of events is thought to occur late in gestation.[8] Many drugs, including glucocorticoids,[9] beta mimetics,[10] and NA872,[11] when administered to the fetus, have been shown to increase surfactant synthesis and secretion. However, the search continues to establish the endogenous factor(s) that stimulates lung maturation and surfactant synthesis in the fetus. Corticosteroids were eliminated as the natural trigger for surfactant synthesis when it was shown that surfactant production precedes the rise in fetal plasma corticoids.[12] On the other hand, it has been shown that human fetal surfactant levels increase[13] at a time in gestation which is preceded by a large increase in serum prolactin levels.[14] In addition, recent evidence suggests that pharmacologic doses of prolactin increase the synthesis of pulmonary surfactant as measured by a rise in phospholipid, lecithin, and dipalmitoyl lecithin concentrations in lung tissue homogenates from the fetal rabbit.[15] In order to determine whether these biochemical changes are associated with a physiologic maturation of the fetal lung, the present study assessed the effect of prolactin on the fetal rabbit pulmonary pressure volume relationship.

Materials and methods

Eight New Zealand white rabbits, with timed pregnancies, were used in these experiments. The time of mating (8:00 to 10:00) was taken as time zero for the calculation of gestational age. Ovine prolactin* was dissolved in hormone solvent composed of 3 mg of phenol and 50 mg of glucose per milliliter in water. In addition, the hormone solvent was employed as the control vehicle. Five pregnant does were anesthetized with sodium pentobarbital (30 to 35 mg/kg intravenously) on Day 24 of gestation. Under sterile conditions, a midline incision was made to expose the fetal rabbits. Approximately half the fetuses were injected, into the rump, with 1.0 mg (0.05 ml) of prolactin. The remainder of

*Supplied by Sigma Chemical Company, St. Louis, Missouri.

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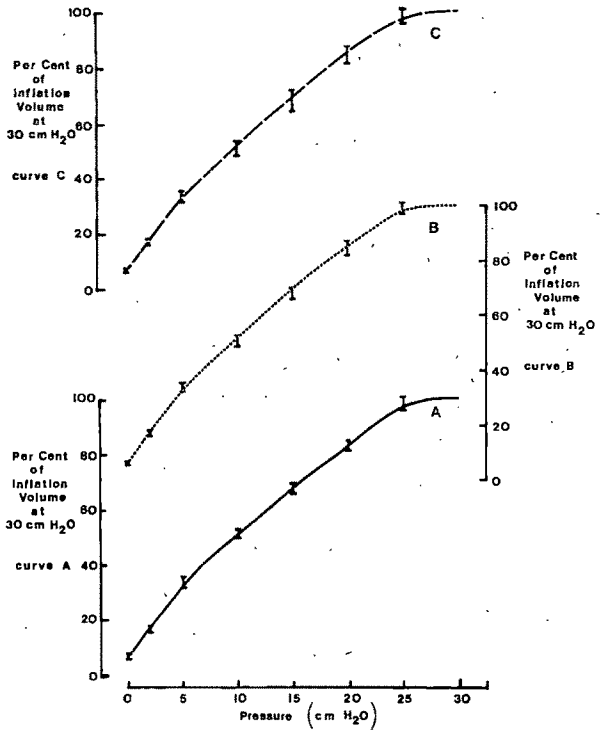


Fig. 1. Pressure-volume relationships in 26 day rabbit fetal lung after treatment of the fetus as follows: *Curve A* = fetal rabbits injected intramuscularly with 1.0 mg prolactin on Day 24 of gestation (N = 12); *Curve B* = fetal rabbits injected intramuscularly with equivalent volume of prolactin control vehicle on Day 24 of gestation (N = 10); *Curve C* = normal fetal rabbits not injected. All values are the volumes retained at the pressures indicated and are expressed as % of the total volume required to inflate the lungs to a pressure of 30 cm of water. Standard deviations of the mean are shown by the vertical bars.

the fetuses served as control subjects and were given an equivalent volume of control vehicle. Following prolactin and control vehicle administration, the abdomen was closed and the doe was allowed to recover. On Day 26 of gestation the doe was killed by means of an effective dose (45 to 55 mg/kg by rapid intravenous injection) of pentobarbital. Subsequently, the fetuses were removed from the doe and prepared for determination of deflation pressure volume curves using the method previously described.[11] Thus, estimation of lung maturation in the prolactin-treated fetuses (N = 12), control (N = 10) fetuses, or normal untreated fetuses (N = 15) obtained from three additional does was made by means of a pressure volume apparatus similar to that previously described.[16] The lungs were inflated to a pressure of 30 cm H_2O held stable for five minutes. At the end of each experiment, fetal body weight, body length, and lung wet weight were determined. Using a similar protocol, experiments were then carried out using older fetuses (Day 28 of gestation).

Results

The effect of ovine prolactin administration to the fetal rabbit on fetal lung maturity, as judged by pressure volume curves, at Day 26 of gestation is illustrated in Fig. 1 (Curve A). Compared with injected control subjects (Curve B) prolactin-treated fetuses did not significantly differ in their pressure volume relationship. Furthermore, the pressure volume deflation curves for these two groups were not significantly different from those of a normal group of the same gestational age, that was not injected with control vehicle (Curve C). Thus, the injection procedure utilized to administer prolactin and control vehicle to the fetuses did not increase fetal lung maturation. Experiments carried out using older fetuses (Day 28 of gestation) gave similar results. However, the pressure volume relationship of the fetal rabbit lungs at Day 28 of gestation resembled the full-term pressure volume profile more than that of the fetal rabbit lungs at Day 26 of gestation. This is expected due to the normally occurring maturation of the lung.[16] In prolactin-treated, injected control, and noninjected normal fetuses, the measures of fetal body length, body weight, lung wet weight, and lung wet weight as a percentage of total body weight were not found to be significantly different (Table I).

Comment

The present experiments in the rabbit indicate that intramuscular administration of a pharmacologic dose of prolactin, on Day 24 of gestation, produced no significant enhancement of lung maturation in the 26 day fetal rabbit lung. In contrast, earlier evidence suggests that prolactin stimulates the synthesis of surfactant in the fetal rabbit lung.[15] Thus, Hamosh and Hamosh[15] found that after fetal prolactin administration there was a significant increase in dipalmitoyl lecithin, the primary constituent of surfactant,[17] in the fetal rabbit lung. The apparent discrepancy between these biochemical data and our physiologic data may be due to several factors. The biochemical method used by Hamosh and Hamosh[15] involved the isolation of surface active material from a lung tissue homogenate.[18] Thus, it is likely that the dipalmitoyl lecithin was derived from both intra- and extracellular sources. The possibility exists that distinct and specific factors are required to initiate the intracellular synthesis and the secretion of surfactant from the alveolar type II pneumocytes. This is consistent with the suggestion

Table I. Physical characteristics of 26 day fetal rabbits

Characteristics	*Normal (no injection)*	*Control (injected with control vehicle)*	*Prolactin (1 mg intramuscularly)*
No. of fetuses	15	10	12
Body length* (cm)	6.85 ± 0.30	7.20 ± 0.25	7.20 ± 0.41
Body weight (gm)	17.38 ± 1.60	18.01 ± 1.96	17.56 ± 2.33
Lung wet weight (gm)	0.46 ± 0.048	0.47 ± 0.056	0.49 ± 0.057
Lung wet weight (% of body weight)	2.64 ± 0.15	2.63 ± 0.26	2.79 ± 0.28

All values are the mean ± standard deviation of the mean.
*Crown-rump length.

that lung maturation and surfactant synthesis could be under multiple hormone control.[15] Thus prolactin may trigger the synthesis of surfactant in type II alveolar pneumocytes, but it may not initiate the secretion of surfactant into the alveolar lumen. Such a proposal could explain the finding of increased amounts of surfactant in lung tissue homogenates of prolactin-treated fetuses, compared to control subjects, while no difference in the pulmonary pressure volume relationship for two similarly treated groups was found. According to this suggestion, the increased amount of synthesized surfactant in the prolactin-treated fetuses would remain intracellular in location. As a result, surface tension at the air-tissue interface of prolactin-treated fetuses would not significantly differ from that in control fetuses. If prolactin induced both the synthesis and secretion of surfactant, one would expect to see a pressure volume relationship in the prolactin-treated fetuses characteristic of more mature fetal rabbit lungs.

On the other hand, prolactin may trigger the synthesis and secretion of surfactant that is defective in its ability to reduce surface tension or prolactin may not be responsible for the induction of surfactant synthesis. The former view is consistent with previous evidence that shows surfactant to be composed of more than dipalmitoyl lecithin[17]; proteins and other lipids are also present in surfactant. It is possible that prolactin stimulates the synthesis and secretion of surfactant that is lacking an important protein component required to effectively reduce surface tension in the alveoli.

In these experiments the use of two control groups was considered essential. Previous experiments suggested that fetal distress was responsible for the production of surfactant at earlier stages of gestation than normally observed.[11] Thus, it is possible that the injection procedure used to administer the prolactin and control vehicle could result in lung maturation. However, the finding that the pressure volume relationships for the injected fetuses are the same as the pressure volume relationship for the noninjected control fetuses suggests that the injection procedure did not cause fetal distress in these experiments. A variety of other differences including nutritional status and housing conditions may contribute to the apparent difference in our data and those of Hamosh and Hamosh.[15] In this regard the effect of the apparently very large litter size of eight fetuses found by Hamosh and Hamosh[15] is unknown. However, it is concluded that the current data do not support a postulated role for prolactin in physiologic maturation of the rabbit fetal lung.

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Classic pages in
OBSTETRICS AND GYNECOLOGY
Lawrence D. Longo, M.D.

Regeneration of the uterine mucosa after delivery, with especial reference to the placental site

JOHN WHITRIDGE WILLIAMS

American Journal of Obstetrics and Gynecology, vol. 22, pp. 664-696 and 793-796, 1931

time there is a good deal of free blood in the superficial layers, associated with a moderate amount of leucocytic infiltration, which, however, is not pronounced unless it is associated with infection. As the puerperium advances a portion of the superficial tissue undergoes necrosis and is cast off with the lochia, but the greater part of the placental site is retained and is gradually cast off or exfoliated as will be explained later.

On the eighth day, the conditions remain essentially the same, except that the placental site has become definitely smaller, but at the same time somewhat thicker than during the first few days. Even at this time, however, not all of the thrombosed vessels have become or-

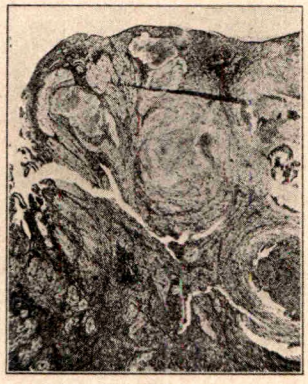


Fig. 22.—Part of placental site seventeenth day postpartum, with undermining at left margin (×18).

ganized, as is shown by Fig. 19. At this time, the placental site is not yet covered by epithelium, which appears to be limited to its margins and to its basal portion. In these locations, however, it is seen that well-developed endometrial tissue is present and apparently is extending beneath the thrombosed vessels which now make up the greater part of the placental site. This is still more clearly shown by Fig. 20, which represents sections from the twelfth day.

A few days later, the placental site is constituted by a dense mass of tissue consisting of obliterated arteries and thrombosed and organized veins, while a good deal of the tissue between them has undergone hyalin degeneration. Figs. 21 and 22 show the conditions in two specimens at the seventeenth day. In the first, the placental site ex-

The events associated with involution of the placental site and other changes in the uterus during the puerperium have interested numerous investigators. William Hunter, who originally described the decidua, observed that it ". . . is an effloresence of the internal coat of the uterus itself; and is therefore shed, as often as a woman bears a child, or suffers a miscarriage. It is of considerable thickness, and one stratum of it is always left upon the uterus after delivery, most of which dissolves and comes away with the lochia" (*An Anatomical Description of the Human Gravid Uterus and Its Contents,* London, 1794 J. Johnson, p 55). Carl Friedlander described the superficial compact and deeper spongy layers of the decidua and stated that placental separation occurred in the deeper part of the former, so that the endometrium regenerated from the glands in the spongy layer. In addition, he demonstrated that while most of the uterine mucosa had regenerated by 4 weeks this did not occur for several additional weeks at the placental site (*Physiol. Anat. Untersuchugen über den Uterus,* Leipzig, 1870). A few years later C. Gerhard Leopold stated that the decidua was cast off post partum and new endometrial glands were derived from serotinal cells interspersed between bundles of myometrial cells (Studien über die Uterusschleimhaut während Menstruation, Schwangerschaff und Wochenbett, Arch. Gynaekol. 11:443, 1877). Emil Ries first suggested that exfoliation of the decidua at the placental site occurs by an undermining of new endometrium (Klinische und anatomische Studien über Zurückbildung des puerperaten Uterus, Z. Geburtshilfe Gynaekol. 24:33, 1892). It was Williams, however, who most completely described the morphologic changes associated with involution of the placental site; his conclusions were based on a study of normal uteri surgically removed from shortly after delivery to the fourth month post partum. He confirmed earlier reports that the cervical mucosa is restored by the end of the first week, and the endometrium, other than at the placental site, is restored completely during the third week. One of Williams' chief contributions was to describe the mechanism of exfoliation of the placental site, and he also showed that exfoliation is not normally associated with inflammation or extensive necrosis. Fig. 22 (see illustration) shows this undermining by endometrium of the thrombosed vessels in part of the placental site.

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Regarding the fate of the placental site, Williams wrote: ". . . six to seven weeks are required for its disappearance, and that it is not effected by absorption in situ, but rather by a process of exfoliation which is in great part brought about by the undermining . . . by the growth of endometrial tissue. This is effected in part by extension and downgrowth of endometrium from the margins of the placental site, and partly by the development of endometrial tissue from the glands and stroma left in the depths of the decidua basalis after separation of the placenta. In general, I am inclined to attach more importance to the former than to the latter mechanism . . . such a process of exfoliation should be regarded as very conservative, and as a wise provision on the part of Nature; otherwise great difficulty might be experienced in getting rid of the obliterated arteries and organized thrombi, which if they remained in situ would soon convert a considerable part of the mucosa into a mass of scar tissue, with the results that after a few pregnancies it would no longer be possible for it to go through its useful cycle of changes, and the reproductive career would come to an untimely

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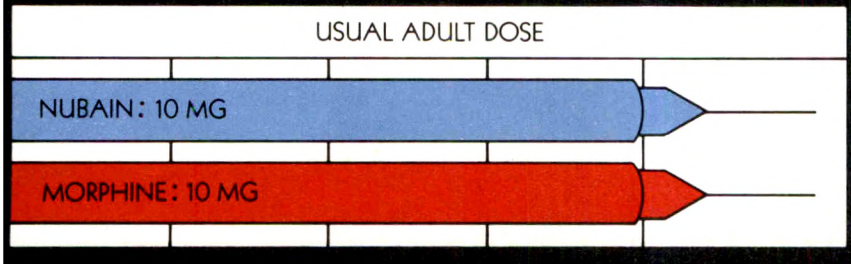


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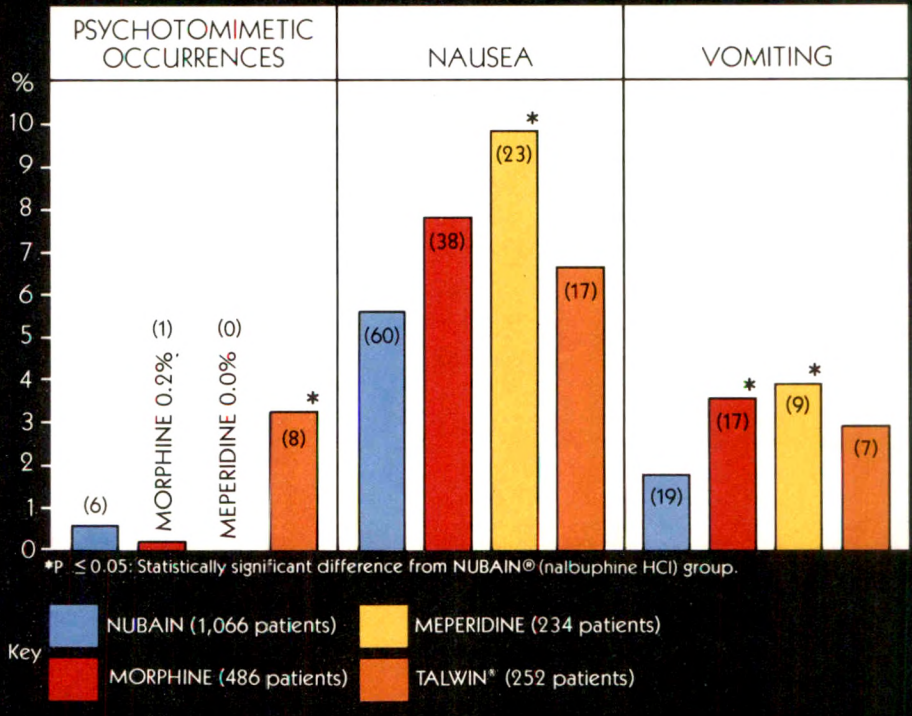
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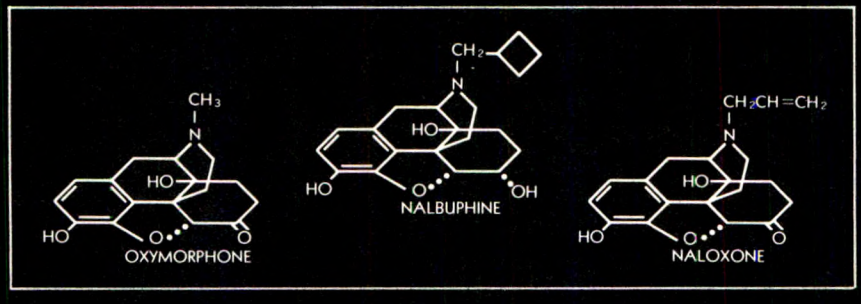
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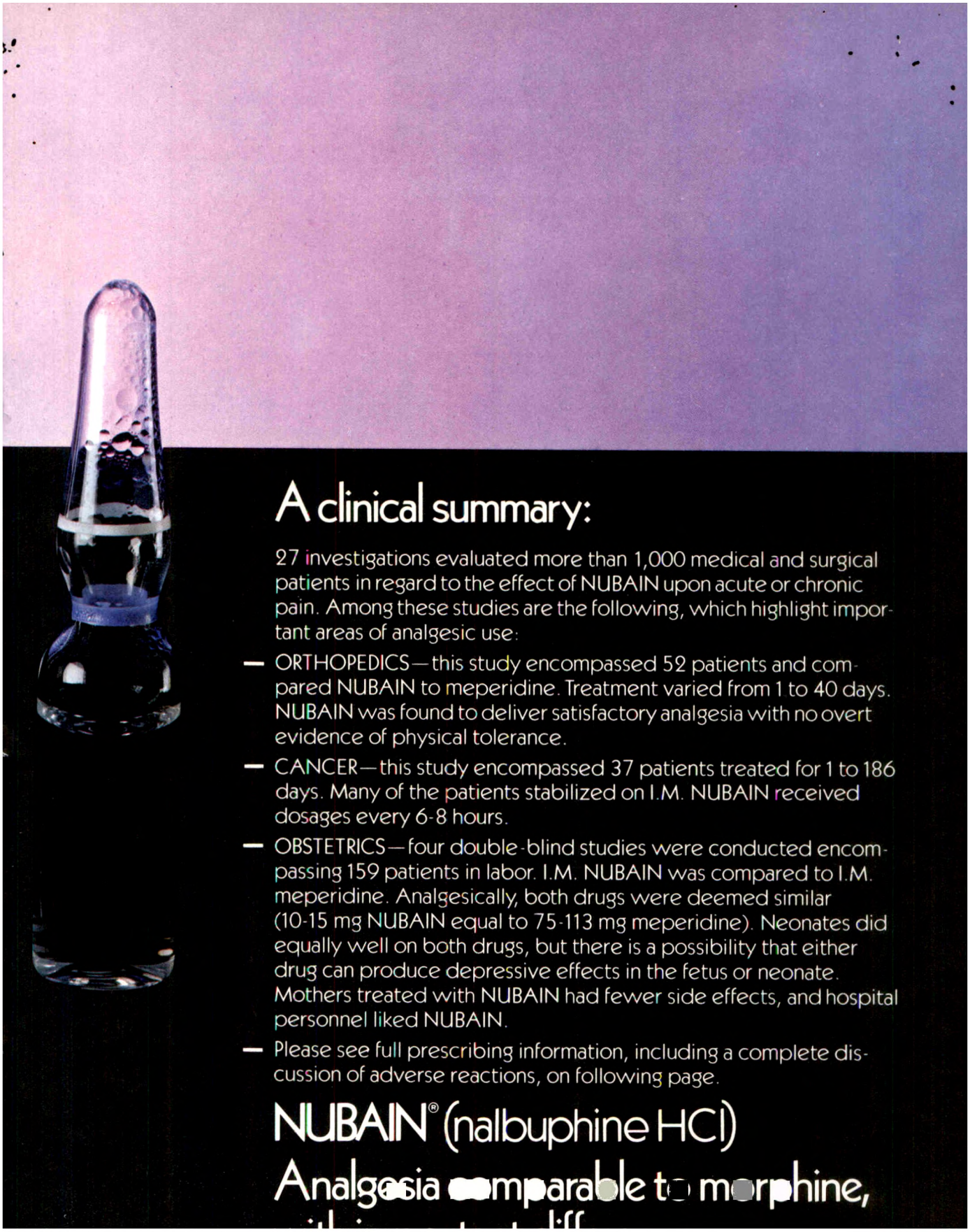
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- CANCER—this study encompassed 37 patients treated for 1 to 186 days. Many of the patients stabilized on I.M. NUBAIN received dosages every 6-8 hours.
- OBSTETRICS—four double-blind studies were conducted encompassing 159 patients in labor. I.M. NUBAIN was compared to I.M. meperidine. Analgesically, both drugs were deemed similar (10-15 mg NUBAIN equal to 75-113 mg meperidine). Neonates did equally well on both drugs, but there is a possibility that either drug can produce depressive effects in the fetus or neonate. Mothers treated with NUBAIN had fewer side effects, and hospital personnel liked NUBAIN.
- Please see full prescribing information, including a complete discussion of adverse reactions, on following page.

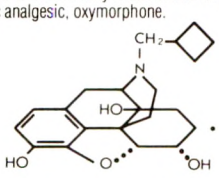
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DESCRIPTION

NUBAIN (nalbuphine hydrochloride) is a synthetic narcotic agonist-antagonist analgesic of the phenanthrene series. It is chemically related to both the widely used narcotic antagonist, naloxone, and the potent narcotic analgesic, oxymorphone.



NALBUPHINE HYDROCHLORIDE

(-)-17-(cyclobutylmethyl)-4,5α-epoxy-morphinan-3, 6α, 14-triol,hydrochloride

• HCl

Each ml of the injectable aqueous solution of NUBAIN contains 10 mg of nalbuphine hydrochloride.

ACTIONS

NUBAIN is a potent analgesic. Its analgesic potency is essentially equivalent to that of morphine on a milligram basis.

Its onset of action occurs within 2 to 3 minutes after intravenous administration, and in less than 15 minutes following subcutaneous or intramuscular injection. The plasma half-life of nalbuphine is 5 hours and in clinical studies the duration of analgesic activity has been reported to range from 3 to 6 hours.

The narcotic antagonist activity of NUBAIN is one-fourth as potent as nalorphine and 10 times that of pentazocine.

INDICATIONS

For the relief of moderate to severe pain. NUBAIN can also be used for preoperative analgesia, as a supplement to surgical anesthesia, and for obstetrical analgesia during labor.

CONTRAINDICATIONS

NUBAIN should not be administered to patients who are hypersensitive to it.

WARNINGS

Drug Dependence NUBAIN has been shown to have a low abuse potential which is approximate to that of pentazocine. When compared with drugs which are not mixed agonist-antagonists, it has been reported that nalbuphine's potential for abuse would be less than that of codeine and propoxyphene. Psychological and physical dependence and tolerance may follow the abuse or misuse of nalbuphine. Therefore, caution should be observed in prescribing it for emotionally unstable patients, or for individuals with a history of narcotic abuse. Such patients should be closely supervised when long-term therapy is contemplated.

Care should be taken to avoid increases in dosage or frequency of administration which in susceptible individuals might result in physical dependence.

Abrupt discontinuation of NUBAIN following prolonged use has been followed by symptoms of narcotic withdrawal, i.e., abdominal cramps, nausea and vomiting, rhinorrhea, lacrimation, restlessness, anxiety, elevated temperature and piloerection.

Use in Ambulatory Patients NUBAIN may impair the mental or physical abilities required for the performance of potentially dangerous tasks such as driving a car or operating machinery. Therefore, NUBAIN should be administered with caution to ambulatory patients who should be warned to avoid such hazards.

Use in Emergency Procedures Maintain patient under observation until recovered from NUBAIN effects that would affect driving or other potentially dangerous tasks.

Use in Children Clinical experience to support administration to patients under 18 years is not available at present.

Use in Pregnancy (other than labor) Safe use of NUBAIN in pregnancy has not been established. Although animal reproductive studies have not revealed teratogenic or embryotoxic effects, nalbuphine should only be administered to pregnant women when, in the judgement of the physician, the potential benefits outweigh the possible hazards.

Use During Labor and Delivery NUBAIN can produce respiratory depression in the neonate. It should be used with caution in women delivering premature infants.

Head Injury and Increased Intracranial Pressure The possible respiratory depressant effects and the potential of potent analgesics to elevate cerebrospinal fluid pressure (resulting from vasodilation following CO_2 retention) may be markedly exaggerated in the presence of head injury, intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, potent analgesics can produce effects which may obscure the clinical course of patients with head injuries. Therefore, NUBAIN should be used in these circumstances only when essential, and then should be administered with extreme caution.

Interaction With Other Central Nervous System Depressants Although NUBAIN possesses narcotic antagonist activity, there is evidence that in nondependent patients it will not antagonize a narcotic analgesic administered just before, concurrently, or just after an injection of NUBAIN. Therefore, patients receiving a narcotic analgesic, general anesthetics, phenothiazines, or other tranquilizers, sedatives, hypnotics, or other CNS depressants (including alcohol) concomitantly with NUBAIN may exhibit an additive effect. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

PRECAUTIONS

Impaired Respiration At the usual adult dose of 10 mg/70 kg, NUBAIN causes some respiratory depression approximately equal to that produced by equal doses of morphine. However, in contrast to morphine, respiratory depression is not appreciably increased with higher doses of NUBAIN. Respiratory depression induced by NUBAIN can be reversed by NARCAN® (naloxone hydrochloride) when indicated. NUBAIN should be administered with caution at low doses to patients with impaired respiration (e.g., from other medication, uremia, bronchial asthma, severe infection, cyanosis or respiratory obstructions).

Impaired Renal or Hepatic Function Because NUBAIN is metabolized in the liver and excreted by the kidneys, patients with renal or liver dysfunction may overreact to customary doses. Therefore, in these individuals, NUBAIN should be used with caution and administered in reduced amounts.

Myocardial Infarction As with all potent analgesics, NUBAIN should be used with caution in patients with myocardial infarction who have nausea or vomiting.

Biliary Tract Surgery As with all narcotic analgesics, NUBAIN should be used with caution in patients about to undergo surgery of the biliary tract since it may cause spasm of the sphincter of Oddi.

ADVERSE REACTIONS

The most frequent adverse reaction in 1066 patients treated with NUBAIN is sedation (381, 36%). Less frequent reactions are: sweaty/clammy (99, 9%), nausea/vomiting (68, 6%), dizziness/vertigo (58, 5%), dry mouth (44, 4%), and headache (27, 3%).

Other adverse reactions which may occur (reported incidence of 1% or less) are:

CNS Effects nervousness, depression, restlessness, crying, euphoria, floating, hostility, unusual dreams, confusion, faintness, hallucinations, dysphoria, feeling of heaviness, numbness, tingling, unreality. The incidence of psychotomimetic effects, such as unreality, depersonalization, delusions, dysphoria and hallucinations has been shown to be less than that which occurs with pentazocine.

Cardiovascular Hypertension, hypotension, bradycardia, tachycardia.

Gastrointestinal Cramps, dyspepsia, bitter taste.

Respiration Depression, dyspnea, asthma.

Dermatological Itching, burning, urticaria.

Miscellaneous Speech difficulty, urinary urgency, blurred vision, flushing and warmth.

DOSAGE AND ADMINISTRATION

The usual recommended adult dose is 10 mg for a 70 kg individual, administered subcutaneously, intramuscularly or intravenously; this dose may be repeated every 3 to 6 hours as necessary. Dosage should be adjusted according to the severity of the pain, physical status of the patient, and other medications which the patient may be receiving. (See Interaction with Other Central Nervous System Depressants under WARNINGS.) In non-tolerant individuals, the recommended single maximum dose is 20 mg, with a maximum total daily dose of 160 mg.

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COMMUNICATIONS IN BRIEF

This section is suitable for reporting results of therapeutic trials, descriptions of new procedures or instruments, and case reports which illustrate a principle. Reports should be limited to seven hundred words and two references. Use of an illustration or table requires a proportionate reduction in total words.

Pulmonary edema associated with magnesium sulfate and betamethasone administration

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MAJOR (MC) USA
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SEVERAL RECENT REPORTS have described acute pulmonary edema in patients treated simultaneously with beta-sympathomimetic agents to stop premature labor and corticosteroids to accelerate fetal pulmonary maturation.[1–3] There were eight cases in Germany involving fenoterol, a case from England involving ritodrine, and a case from Boston, involving terbutaline. Both betamethasone and dexamethasone have been used as the glucocorticoid drug in these 10 cases. There was one maternal death. Recently magnesium sulfate has been advocated as a tocolytic agent.[4] This report describes acute pulmonary edema in two patients treated with magnesium sulfate and betamethasone.

In Case 1, L. N., a 37-year-old woman, gravida 9, para 7, abortions 1, with six living children, had an uneventful twin pregnancy until 34 weeks' gestation when she had spontaneous rupture of the membranes with no labor. Her past medical history was unremarkable with no known rheumatic fever; a cardiac history included a murmur detected 18 months prior to pregnancy. Cardiologic evaluation including echocardiography concluded that it was a benign flow murmur.

Physical examination was normal. Vital signs were: blood pressure, 130/80; respirations, 16/min; pulse, 76/min. The lungs were clear to auscultation and percussion. The heart had a regular sinus rhythm, with no murmurs. Hematocrit was 27.2%. After amniocentesis revealed a lecithin/sphingomyelin (L/S) ratio of 1.2/1, she was treated with 2 ml Celestone* intramuscularly (6 mg betamethasone acetate and 6 mg betamethasone phosphate) and was started on a regimen of magnesium sulfate, as described by Steer and Petrie,[4] to prevent labor. Forty-eight hours later, an elective cesarean section was performed following epidural anesthesia due to transverse lie of both fetuses. Forty-five minutes after operation, respirations were noted to be labored. She complained of shortness of breath and developed a cough with lower lobe rales and wheezes, with x-ray evidence of bilateral infiltration, consistent with pulmonary edema.

The patient initially developed wheezing and dyspnea, which was felt to be an asthmatic type of reaction, and aminophylline treatment was instituted. A chest roentgenogram, however, showed clear evidence of pulmonary venous hypertension and pulmonary edema. The patient had a good response to diuretic therapy. The remainder of the hospital course was normal. Both infants did well and were discharged with the mother.

In Case 2, J. C., a 22-year-old woman, gravida 2, para 0, abortions 1, had an uncomplicated pregnancy until 33 weeks' gestation when she developed severe pre-eclampsia with blood pressure of 150/100, proteinuria (4+), edema (2+), and hyperreflexia (3+). L/S ratio was 1.0/1 and she was treated conservatively with bed rest and phenobarbitol. She developed a pruritic rash and the phenobarbitol was stopped. One week later the blood pressure was up to 148/104, with proteinuria (2+) and hyperreflexia (3+). She was transferred to Women's Hospital, Long Beach, at this time in premature labor.

Past medical history revealed no major medical problems, including a totally negative cardiac history. Vital signs consisted of: blood pressure, 160/110; respirations, 18/min; temperature, 98.4° F; pulse, 80/min. Pertinent physical findings included lungs that were clear to percussion and auscultation. Heart examination revealed normal sinus rhythm with no murmurs. The fundal height was 32 cm, with fetal heart tones

*Schering Corp., Kenilworth, New Jersey.

The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

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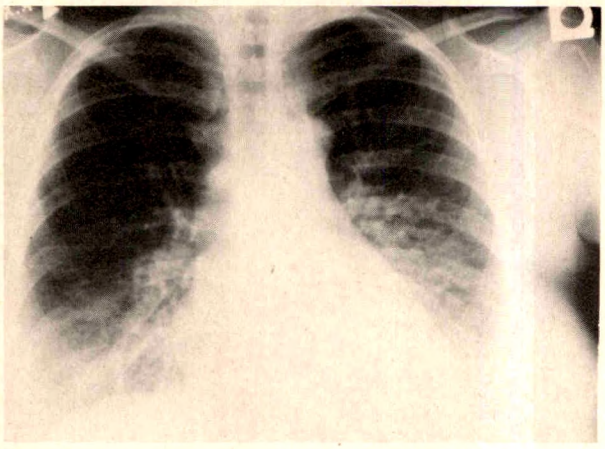


Fig. 1. Case 2. Chest roentgenogram demonstrating pulmonary edema and congestive heart failure.

of 144/min. The cervix was 50% effaced and closed with a ballotable vertex presentation. There was (2+) edema of the extremities with no cyanosis. There was deep tendon hyperreflexia (3+) with no clonus. Hematocrit was 27.2%.

On the monitor, contractions were every 3 to 5 minutes. The baby's heart rate pattern was reactive with no decelerations.

A repeat L/S ratio was 1.0/1. Magnesium sulfate was administered as described by Steer and Petrie,[4] as a tocolytic agent and to increase the seizure threshold.

With pre-eclampsia worsening and premature labor present, a decision was made to administer betamethasone, with the patient continuously on the fetal monitor. Celestone (12 mg) was administered intramuscularly. Contractions stopped and blood pressure ranged from 120 to 130/80 to 90. Deep tendon reflexes (1+) and proteinuria (1+) remained. Fifteen hours after the second dose of 12 mg Celestone she complained of increasing difficulty in breathing and cough.

Physical findings then showed a blood pressure of 164/98; respirations, 30/min; pulse, 112/min; temperature, 98.8° F. Bibasilar rales were heard and cardiovascular examination was consistent with congestive heart failure with an S_3 and S_4 gallop present. Reflexes (2+) and edema (2+) were present.

Chest roentgenography was consistent with pulmonary edema and congestive heart failure (Fig. 1). The maximum serum magnesium level was 5.6 mg/100 ml. Echocardiogram revealed no evidence of cardiac disease. A total of 4,400 ml of 5% dextrose in lactated Ringer's solution and 5½% dextrose in ½N saline had been given intravenously with nothing by mouth, and total urinary output was 2,800 ml. A Schwann-Ganz catheter was inserted. Right atrial pressure was 18 mm Hg; right ventricle, 40/15 mm Hg; pulmonary artery, 40/25 mm Hg; wedge pressure, 30 mm Hg. She was treated with Lasix, 40 to 80 mg as needed, to lower wedge pressure, digitalis, oxygen, and fluid restriction, with resolution of congestive heart failure over the next 16 hours. Labor was induced the following morning, with subsequent vaginal delivery of a viable, 2,015 gram male infant, Apgar scores 8 and 9. Her postpartum course was normal.

The effective use of magnesium sulfate as a tocolytic agent has been described.[4] At Women's Hospital, Long Beach, we have used this drug recently for the treatment of premature labor and it appears to be reasonably effective. The mechanism of its action on the uterine musculature is unknown but may be due to an inhibitory effect on calcium transport in the muscle cell. Magnesium sulfate has been shown to have a profound effect of the cardiovascular system in the nonpregnant human.[5] There is a decrease in peripheral vascular resistance, and in hypertensive patients a decrease in mean arterial blood pressure has been shown. There is also an increase in cardiac index and often an increase in heart rate. This increased stroke volume and cardiac output must result in increased cardiac work. Similar cardiovascular changes have been attributed to beta-sympathomimetic agents.[2]

Corticosteroids have myriad diverse effects but little known direct effects on the cardiovascular system. The role they may play is uncertain.

Corticosteroids and tocolytic agents (magnesium sulfate, ritodrine hydrochloride, and intravenous alcohol) have been used extensively in our hospital, and only these two cases of pulmonary edema and congestive heart failure have been found. These cases are the first reported of the association of magnesium sulfate and corticosteroids with acute pulmonary edema in pregnant patients. Previous reports in the literature strongly implicate various beta-sympathomimetic amines as the causative agents, with the role of the corticosteroid uncertain. Although there is a clinically observed association, there is no clear physiologic basis to implicate the steroids in this process. At least in some pregnant patients magnesium sulfate appears to have cardiovascular effects that are similar to those of beta-mimetic amines. The low incidence of this complication leads to speculation about other predisposing factors in those patients who develop acute pulmonary edema. Both of our patients were anemic; one had a twin gestation and the other, severe pre-eclampsia. Some of the reported cases had predisposing factors, and in the fatal case from Germany the patient appeared to have organic heart disease.

This report of pulmonary edema associated with magnesium sulfate and corticosteroid administration, used to improve fetal outcome where premature delivery is imminent, should point to the possibility that some maternal risk may be involved. When using beta-mimetic amines or magnesium sulfate in association with corticosteroids (or perhaps alone) this complication must be kept in mind.

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Tuberculous peritonitis and endometritis mimicking a "frozen pelvis"

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A CASE OF genital tuberculosis with tuberculous peritonitis is reported.

A 15-year-old black female patient, gravida 0, para 0, ABO, presented with a 3 month history of a progressively enlarging pelvic mass, amenorrhea, a 15 kilogram weight loss, anorexia, malaise, fatigue, and lower abdominal discomfort. She denied all history of fevers, chills, night sweats, diarrhea, constipation, increasing abdominal girth, tuberculosis in the family, or foreign travel. Physical examination was unremarkable except for a very firm mass filling the cul-de-sac, extending to both pelvic side walls and reaching the level of the umbilicus.

Laboratory data on admission included negative pregnancy test, absence of fetal heart sounds by Doptone, hemoglobin of 9.3, sedimentation rate of 64, and a leukocyte count of 5,200, with normal differential. The chest x-ray was normal, and a B-mode ultrasound scan of the abdomen revealed a complex, sharply marginated, predominantly solid pelvic mass extending superiorly several centimeters above the umbilicus and laterally to involve both adnexal regions (Figs. 1 to 3). The acoustic characteristics of the mass suggested ovarian neoplasm or uterine sarcoma. An intravenous urogram demonstrated an extrinsic impression on the dome of the bladder. A barium colon examination showed deviation and narrowing of the bowel lumen. The margin of the bowel was serrated, with a "thumbprint" appearance characteristic of edema, hemorrhage, or inflammation of the bowel wall (Figs. 4 to 6), without mucosal invasion, fixation, or rigidity.

Examination under anesthesia confirmed the presence of a "frozen pelvis." A dilatation and curettage revealed caseating granulomas. At laparotomy, multiple grayish nodules were seen studding the peritoneal surfaces and bowel, with matted bowel completely obscuring the pelvis. Biopsy of several of the

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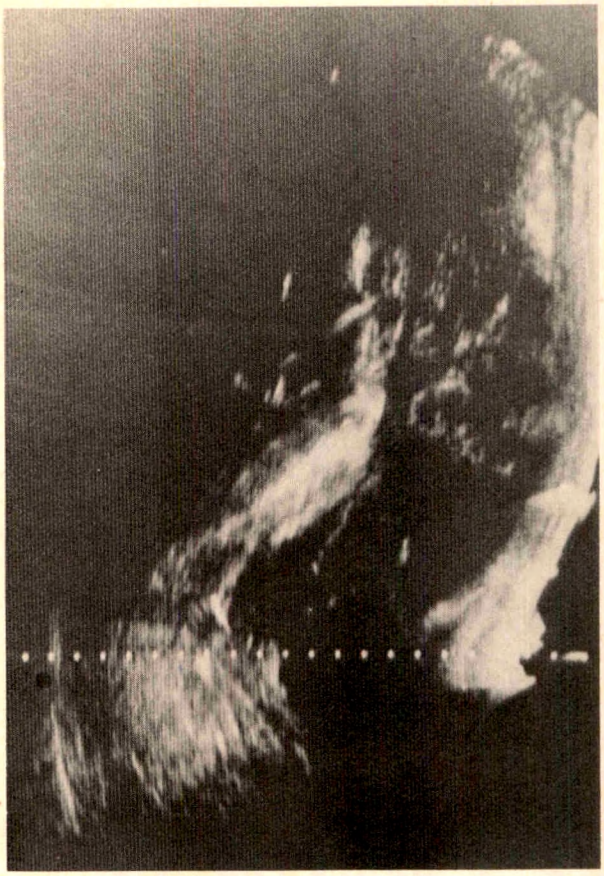


Fig. 1. Longitudinal scan of the pelvis 1 cm to the right of midline. Markers delineate the interface between the mass superiorly and the bladder inferiorly.

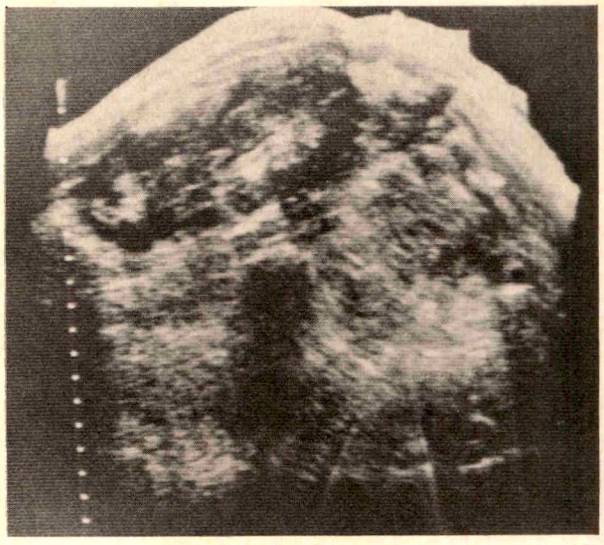


Fig. 2. Transverse scan of the abdomen at the level of the umbilicus. Markers delineate the right lateral margin of the mass which extends across the midline. The superior portion of the mass is predominantly solid.

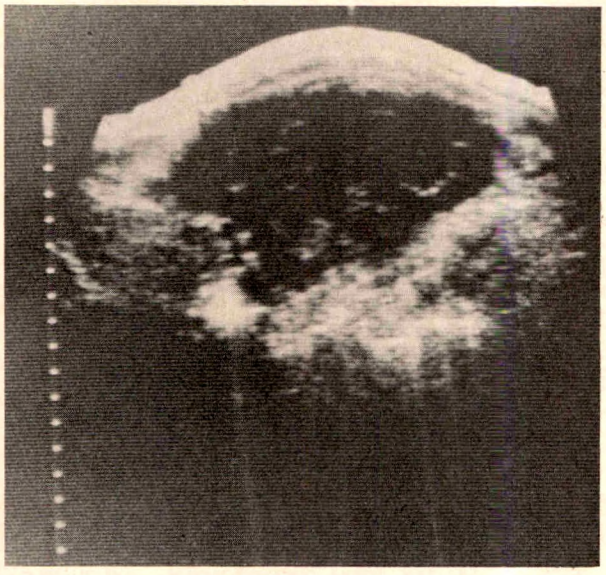


Fig. 3. Transverse scan of the pelvis 5 cm above the symphysis pubis. The inferior portion of the mass has cystic elements with scattered echoes.

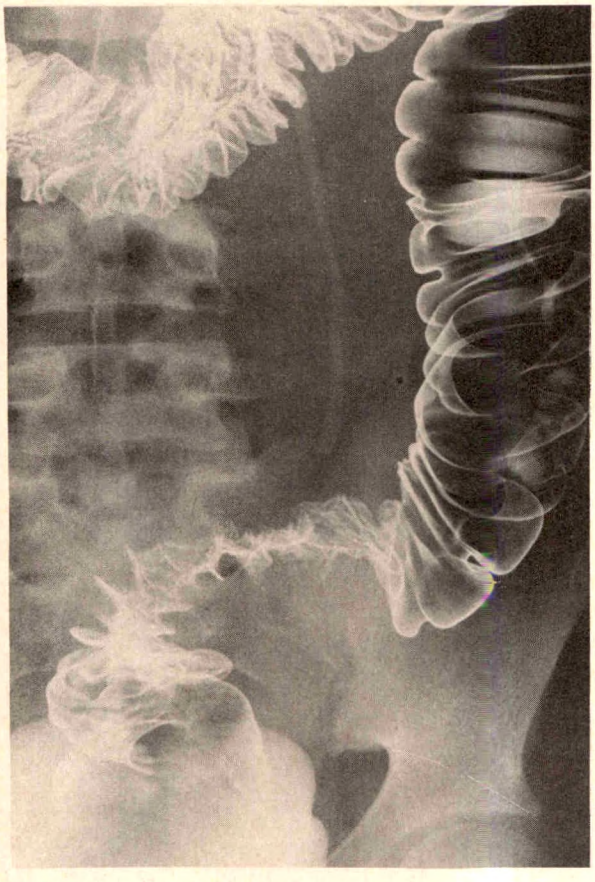


Fig. 4. AP view from the barium enema showing elevation and narrowing of the sigmoid colon. There is residual contrast in the bladder and left ureter.

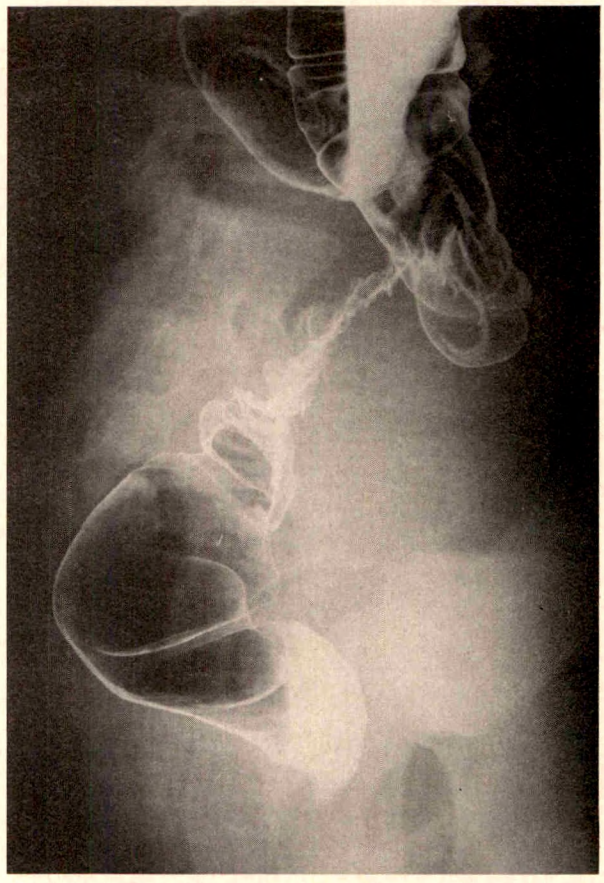


Fig. 5. Lateral view of the colon showing a large pelvic mass between the bladder and sigmoid.

nodules revealed caseating granulomas. Both endometrial and peritoneal tissue were positive for acid-fast bacilli with Ziehl-Nielsen stain, and final culture revealed *Mycobacterium tuberculosis*. Multiple cultures of sputum, nasogastric aspirate, and urine were negative for *M. tuberculosis*. Postoperatively the patient was begun on isoniazid 300 mg/day and ethambutol 25 mg/kg per day and recovered uneventfully. An intermediate strength PPD was strongly reactive on the second postoperative day and liver-spleen and bone scans were within normal limits. Three months postoperatively the patient felt well, and had resumed all normal activities; the abdominal mass had disappeared. The ethambutol dosage was decreased to 15 mg/kg per day then, and a 2 year course of double antibiotic therapy was planned.

This disease is seen in young female patients (2:1 F/M ratio), with abdominal pain, fever, weight loss, ascites, and a mass. Fever is present but episodic. The peritoneal exudate may be scanty, and is culture positive if enough fluid is submitted (83% with 1 L cultured.[1] Skin test for tuberculosis is positive in 100% of the cases, but chest x-ray is frequently normal. A mass is found in 50% of cases. Diagnosis is made by percutaneous or laparoscopic needle biopsy, or preferably by exploratory laparotomy.

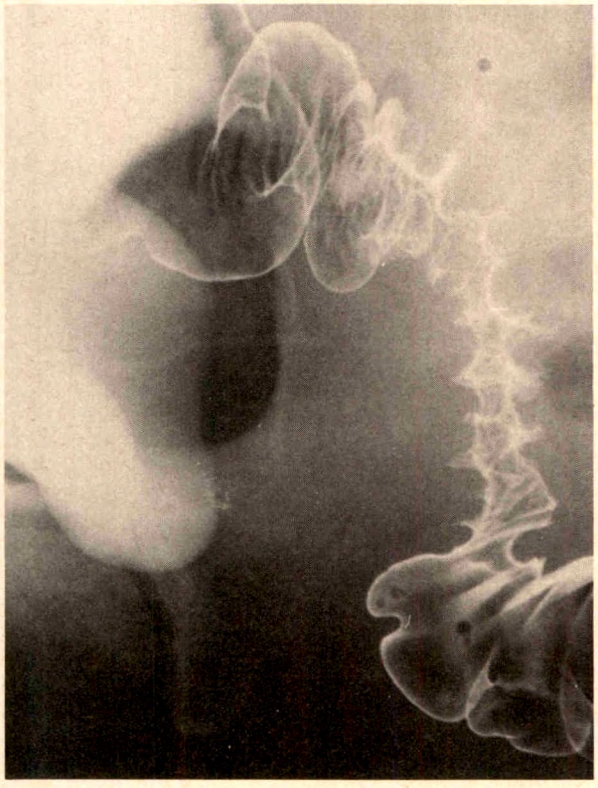


Fig. 6. Oblique view of the sigmoid colon showing the serrated margin and "thumbprinting" without mucosal destruction. There is residual contrast in the bladder and left ureter.

Management consists of a 2 year course of antituberculosis chemotherapy with isoniazid and ethambutol. Rifampin is reserved for resistant organisms. The addition of steroids cannot be supported by the available data.

The prognosis, once poor with less than a 50% 5 year survival, is good, with few reported deaths once antituberculous therapy is begun. Surgical treatment is indicated when chemotherapy fails to decrease the size of the tuboovarian abscesses after 2 months, when there is recurrence of endometrial tuberculosis after 1 year of antimicrobial therapy, when patients are over 40 and will not continue long-term therapy, and when there are fistulas which fail to heal.[2] If tubal patency is documented by hysterosalpingogram, prolonged isoniazid therapy might be advisable. Attempts at tuboplasty are doomed to failure; the prognosis for fertility is generally hopeless, with only 31 documented term pregnancies in patients with genital tuberculosis.

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Pregnancy in a woman with xanthinuria: Study of amniotic fluid uric acid

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XANTHINURIA is a rare metabolic disease in which, due to the deficiency of xanthine oxidase, very low levels of uric acid are found in the blood and in the urine, while abnormally high quantitites of xanthine are present in the circulation and eliminated through the kidney. Fewer than 20 cases have so far been described in the literature,[1] the main reason probably being the fact that the condition is asymptomatic except for the occasional formation of xanthine stones in the bladder.

To our knowledge no cases of this condition have been described in pregnancy.

D. C., 22 years of age was first seen on March 10, 1975, in week 12 of pregnancy. She had already had two previous pregnancies: the first ended spontaneously at week 36 and the male infant (2,100 grams) died 72 hours later, probably because hyaline membrane disease. The second pregnancy terminated spontaneously at week 26 and the small baby died soon afterward. Because of the obstetric history and also because of a certain opening of the cervical os, a cerclage was performed in week 15 of pregnancy. Findings of the routine examinations were all in the normal range except for serum uric acid, which was 0.6 mg/100 ml. Other assays were 0.3, 0.5, and 0.7 mg/100 ml (mean 0.52 mg/100 ml). Mean urinary uric acid was 50 mg/24 hours (range 20 to 75 mg/24 hours). Total purine excretion (expressed as milligrams of uric acid) was 526 mg/24 hours (range 405 to 602 mg/24 hours). Urinary oxypurines were 2,730 μmol/24 hours (range 2,100 to 3,050 μmol/24 hours). A diagnosis of xanthinuria was therefore made; the parents, one sister, and one brother of the patient were examined but normal values were found. In week 34 an amniocentesis was performed and 15 ml of amniotic fluid, slightly contaminated with blood, were recovered. Uric acid in the sample was 2.8 mg/100 ml. In week 37 the amniocentesis was repeated and the fluid was grossly contaminated with blood; since an ultrasonogram showed that the placenta was inserted in the anterior uterine wall, no more amniocenteses were attempted. The pregnancy went uneventfully to term, after the cerclage was removed in week 38. The patient gave birth spontaneously to a female baby, in good condition, who weighed 3,850 grams on September 23, 1975. Amniotic fluid was recovered at the beginning of labor through an intrauterine catheter. In this sample uric acid was 8.2 mg/100 ml. Some colostrum was recovered in the first days of puerperium but the sample could not be examined for

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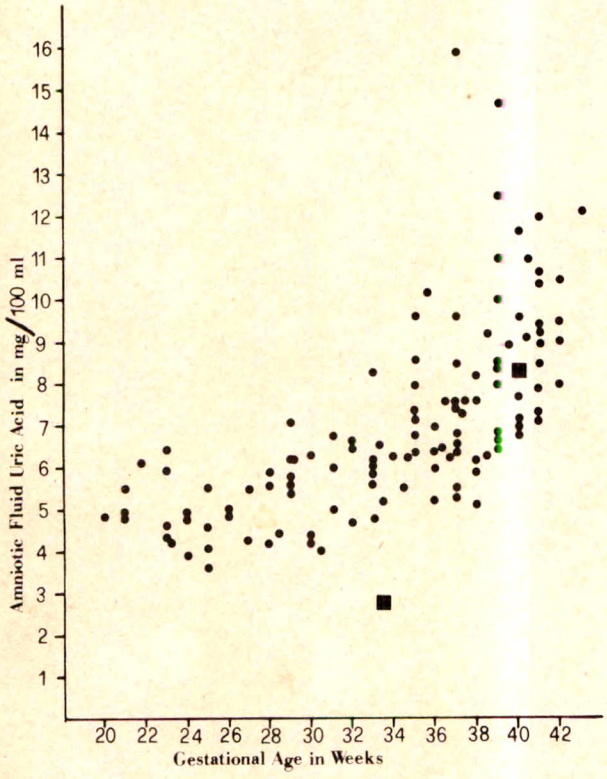


Fig. 1. Uric acid levels in amniotic fluid (■ indicates values observed in the patient with xanthinuria).

xanthine oxidase activity because of technical reasons. Serum uric acid of the newborn infant was 7.5 mg/100 ml.

The first case of xanthinuria in pregnancy has been presented. The pregnancy seemed not to be affected by the condition, and the previous perinatal losses of the patient were apparently due to a different cause.

The study of the amniotic fluid, however, offered interesting information in regard to the origin and levels of uric acid. Uric acid is known to be present in the amniotic fluid in increasing quantities from the beginning to the end of pregnancy.[2] The values observed in our laboratory in cases of normal pregnancy are presented in Fig. 1. The level of amniotic uric acid in the patient with xanthinuria was about half of the mean value observed in normal pregnancies at week 34; the level found at term was within the normal range.

Since no maternal contribution to the uric acid found in the amniotic fluid was possible, it seems logical that at term, when the major mechanism for amniotic fluid formation is fetal urination, normal values were found, whereas 6 weeks earlier, when maternal participation is supposedly more important, a much lower level than normal was observed. Nevertheless, the presence of uric acid in the amniotic fluid at this stage of pregnancy probably shows that fetal urination is already present and might account for up to 50% of amniotic fluid formation.

We thank Dr. Edward W. Holmes, Jr., Assistant Professor of Medicine, Duke University Medical Center, Durham, North Carolina, for his advice and help.

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CORRESPONDENCE

Diploid nuclear replacement in mature human ova with cleavage

To the Editors:

We have read with interest and, I am afraid, some distress the recent article by Dr. Landrum B. Shettles entitled "Diploid nuclear replacement in mature human ova with cleavage" (AM. J. OBSTET GYNECOL. 133:222, 1979). I am sure your reviewers were aware of the potential importance of Dr. Shettles' claim—that he had, in fact, replaced the nucleus of a human oocyte by a nucleus isolated from a spermatogonium with subsequent successful division and early development. Given the fact that cell biologists have been attempting nuclear replacement in mammalian ova unsuccessfully for many years, one would think that the review process would have been unusually rigorous, with careful examination of the available evidence.

Several specific points should be made concerning the nature of the evidence presented by Dr. Shettles:

1. Your reviewers failed to recognize that Dr. Shettles, in his Fig. 1, presented a biologically impossible combination of morphologic features. The first polar body is extruded by the oocyte after the resumption of meiosis, which is invariably accompainied by germinal vesicle breakdown. This means that the nucleus is no longer enclosed by a nuclear envelope and, as such, is not identifiable within the cytoplasm. The chromosomes themselves appear in the periphery of the cytoplasm in various configurations and can be identified by special stains. On this basis alone, the reviewers should have questioned the claim that Dr. Shettles extracted a nucleus from an egg which had released its first polar body.

2. Dr. Shettles claims to have removed the zona pellucide in preparation for piercing the oocyte with a micropipette during aspiration of the intact nucleus, yet the photograph of the oocyte from which the nucleus was extracted (Fig. 4) includes a zona pellucida.

3. Dr. Shettles claims to have removed nuclei from spermatogonia by microsurgical dissection. Those with extensive experience with microsurgical techniques would insist that isolation of individual nuclei by this techniques is highly improbable. In any case it certainly must be documented to be credible. No details as to the actual approach used are included in the manuscript.

4. Finally the photograph contained in Fig. 6 labeled "living morular stage of ovum" is most likely a degenerating egg. In the absence of morphologic documentation of the presence of nuclei in the individual "blastomeres," one would have to assume that it is such.

It is difficult to understand how a manuscript on such a potentially important subject which contains not only biologic inaccuracies but also incomplete documentation could be considered for publication by a journal which supports the concept of peer review.

Luigi Mastroianni, Jr., M.D.
William Goodell Professor and Chairman
Don P. Wolf, Ph.D.
Associate Research Professor of Obstetrics and Gynecology and of Biochemistry and Biophysics
Department of Obstetrics and Gynecology
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Reply to Drs. Mastroianni and Wolf

To the Editors:

In regard to any unsuccessful attempts by cell biologists to replace nuclei in mammalian ova, my experience with microdissecting and micromanipulating apparatus began in 1935 while working for the doctorate in cytogenetics, with exchanging the nucleus, food vacuoles, and certain granules between the amoeba and paramecium. Work along these lines began with the human oocyte in 1951 and has been continued to the present time. Details of observations are presented in the atlas, *Ovum Human,* and in some 30 other published papers.

In gathering material on mammalian ova for the *Handbook of Biological Data* by invitation for the National Research Council, Washington, D. C., in 1956, I learned that in all mammals, with the exception of the dog and horse, at the time the mature ovum (secondary oocyte with the first polar body extruded) is ready for release from the mature ovarian follicle, the double-stranded chromosomes are arrested at the metaphase II on the maturation spindle. With phase-contrast microscopy with the ovum denuded of all the corona radiata and granulosa cells through the enzymatic action of the follicular fluid at body temperature, the ooplasm is sufficiently translucent to permit visualization of the chromosomes on the maturation spindle. With experience, one does not have to employ any special stains, as are apparently required by these critics, in order to locate the aggregate of chromosomes for aspiration. In the event the egg is penetrated by the entire fertilizing spermatozoon, meiosis resumes with

the first polar body already formed, after which the second body is released. When one ascertains the order of events carefully, no "biologically impossible combination of morphologic features" is encountered. They should set the sequence of events straight.

Their criticism regarding the zona pellucida is misrepresenting and incorrect. The zona pellucida removed from the oocyte illustrates the high degree of elasticity of this pellucid membrane and how it may be pierced and yet remain intact upon aspiration of the chromosomes from within the ooplasm. No statement or claim is made that the zona pellucida has to be removed for enucleation. The paper speaks for itself.

In the "Communication in Brief," it is simply stated that the spermatogonial nuclei were dissected free and taken up in the micropipettes. Glass needles were employed. One skilled in microsurgical techniques with micropipettes possessing lumina of only a few microns and glass needles is aware of how this is done. Armchair speculation does not afford the insight.

Inspection of the morula readily reveals chromosomes and chromatin configurations in the nuclei of the blastomeres. Variation in cell size arises when the mitoses become asynchronous. At a given focal level, not all cells are in sharp focus; however, this does not reflect degeneration.

The National Library of Medicine Literature Search (1972 to 1978 inclusive) shows one review by Dr. Mastroianni for 1975, concerning the physiology of the oviduct in cattle and the monkey. No original observations on the human oocyte are listed. Consequently, I fail to see the basis for his assuming the role of final assessor. This quotation appears to be very apropos: "Judge ye not, lest ye be judged." In *Science News*, March 3, 1979, p. 3, Dr. Pierre Soupart stated, "I am also very surprised that the points I am making have escaped Dr. Mastroianni's scrutiny."

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Fetal movements associated with fetal heart rate accelerations and decelerations

To the Editors:

I am referring to the interesting investigations reported by Drs. Timor-Tritsch, Dierker, Zador, Hertz, and Rosen, about fetal movements (FM) associated with fetal heart rate (FHR) accelerations and decelerations (Am J. Obstet. Gynecol. 131:276, 1978).

They say that in their study of 23 low-risk pregnant patients decelerations following accelerations were quite common; they were noted to follow 66.7% of the FHR accelerations; it also appears that, if the duration of the FM increases of 1 to 3 seconds (or longer), correlation of acceleration and deceleration increases from 44.1 to 73.8%. The authors defined deceleration as a decrease of the FHR of at least 6 beats per minute below the baseline; this is established as the average FHR in the 20 seconds prior to each FM.

In general, analysis of the records is often difficult, as Curran,[7] from Glasgow, confessed, despite his great experience on the subject. Kariniemi and Hukkinen[2] advised quantification of the antepartum FHR variability by fetal magnetocardiography and direct electrocardiography. Krebs and Tetres[3] believed that external systems employing ultrasonographic and phonocardiographic recording cannot give FHR variability accurately and may show an apparent increase in variability.

In the splendid tracing of the authors (Fig. 3) we can really see that the basal line goes down after going up. But, in our judgment, it is difficult to ascertain if it goes down under the initial level, because the tracing before the rising of the basal line is not shown. We do not know exactly the height of the basal line before the registered FM. It is necessary to take into consideration that the paper speed was 25 mm/sec. Besides, the authors confess that with the methodology used (tocodynamometer placed on the maternal abdomen) not all the FM are recorded.

The decelerations above mentioned by Timor-Tritsch and associates are observed in normal pregnant women, prior to birth, in association with FM; they are of small amplitude and short duration; they usually indicate fetal well being.

They are quite different from the decelerations that very frequently are observed during labor and delivery: the early decelerations, the late decelerations, and the variable decelerations known by all obstetricians. They must not be confused with the decelerations observed in the antepartum stress test (oxytocin challenge test).

To the decelerations so well described by the authors of the Cleveland Metropolitan General Hospital it is quite necessary to give another name, different from this response, and because they disappear after the administration of atropine, they might be called *small gravidic decelerations of the FHR by vagal stimulation with baseline variability*.

In our country, together with Prof. Josué A. Beruti and Dr. Jorge Diradourian or alone, for many years, we have been working on the registration of the uterine contractions and FM with external hysterodynamography; this is why we are making this commentary because in a few weeks we are presenting two papers on this subject to the Obstetrical and Gynecological Society of Buenos Aires.

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Reply to Dr. Leon

To the Editors:

It seems to be true that with the increase of the duration of the fetal movements (FM) we observe a larger percentage of deceleration of the fetal heart rate FHR following the acceleration. With FM of very short duration (less than 1 second) we observed that these might not be associated with changes in the FHR or, if the origin of the movement is a deep breath or a sigh (as observed with the real-time ultrasound scanning), there might be only a deceleration of the FHR. We did not include in our article movements that lasted 1 second or less. If we look at the decelerations following an acceleration it seems that the less mature the fetus is, the deceleration appears to be more prominent compared to the amplitude and duration of the preceding acceleration.[1] FM prior to 25 weeks seem to be associated with a relatively marked deceleration following an acceleration with a very small amplitude. This observation gains support from the recent work of T. Wheeler and Murrils.[2]

As to the baseline FHR, this was selected as an average of the rate during the 20 seconds prior to the movement. It was obvious from the 1,541 movements analyzed during the study that the baseline FHR could easily be determined and that any increase in the FHR associated with FM was recognized and classified by our definitions.

We agree with Dr. Leon that the decelerations mentioned in our article should not be mistaken for antepartum or intrapartum decelerations or decelerations occurring with contractions of the uterus. We speculated upon the physiologic basis of their occurrence and we feel that these decelerations reflect normal central and peripheral nervous system function.

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The prevention of cervical cancer

To the Editors:

An informative article on the prevention of cervical cancer, "Risk of cervical cancer among an electrocoagulated population," by Tapani Kauraniemi, Ulla Räsänen-Virtanen, and Matti Hakama, appeared in THE JOURNAL in the July 1, 1978, issue on page 533. This article was interesting to me since, in 1932, Dr. Willard R. Cooke, professor of obstetrics and gynecology at Texas University School of Medicine, showed me an infected cervix. He emphasized the importance of cauterization of all cervices with any kind of lesions. He showed us how to do "whole-area cauterization," since the streak method leaves scar tissue between the streaks. The whole area is cauterized.

At Dr. Cooke's suggestion, a "cervicitis" clinic was established in the City and County Hospital and in the Obstetrical and Gynecological Research Institute, Houston, Texas. For more than 40 years, special "cervicitis" clinics and treatment programs have been set up in the gynecology clinics. The cancer clinic and the cervicitis clinic were held in the same part of the gynecology clinic, with red ink used on the chart when the cervix was treated. With this red writing indicating the cases with treated cervices, one could tell which patient has a cauterization, conization, or coagulation (freezing) of the cervix. I have worked in both the cancer and the cervicitis clinics for about 30 years. I have determined that those women in whom the cervix was cauterized seldom had to be referred to the cancer clinic, substantiating the report of Kauraniemi and associates. More than 50,000 patients have been treated in these clinics.

Our group, who "popularized the Papanicolaou smear" for Drs. Trout and Papanicolaou, fully agrees that cauterization of the cervix is many times more important than the present-day mass screening with the Papanicolaou smear. As this article stated, "The potential effect of electrocoagulation in the reduction of cervical cancer may be of major importance and may even exceed the effect of organized mass screening programs practiced all over the world." This statement has been substantiated in my practice of gynecology for over 41 years. Cauterization of the cervix is a more important operation than most hysterectomies. Before performing hysterectomy, we make sure the cervix is clear of all lesions. In private practice, one price was set for cauterization and all of the follow-up so that the patient would return and we could see what happened to the cervix years later. In over 5,000 cauterization, conizations, coagulations, and cryocauterization, not one patient has developed cervical cancer. Lugol's staining and biopsies were routinely utilized in all cases. Dr. Emil Novak, of Baltimore, had a Henslman's colposcope sent to our clinic for studying the cervix. Later several brands of colposcopes were used. For the past 5 years we have made colposcopes with an ordinary dissecting microscope, turned down, and the 1975 strong cool-light sources, a colposcope costing less than $500.

These cervicitis clinics presented an entire exhibit at a May, 1945, meeting in Atlantic City on "Cervicitis: The Lesions and Their Treatments." There were about

150 5-by-7 colored photographs shown. Other scientific exhibits on cervicitis have been presented all over America. In 1962, an article was published, "A simple, self-administered treatment for the prevention of and the destruction of cervical ulcers and pre-cancerous lesions" (Med. Rec. Ann. 55:200, 1961). Here for the first time a method, suitable for use by the patient, of eliminating cervical dysplasia of high and low degrees, carcinoma in situ, ectropions, and ulcers of the cervix and vagina was presented. In 1967, a "Letter to the Editor" also described how a powder, instilled by the patient, at home, with an applicator, could prevent cervical cancer (AM. J. OBSTET. GYNECOL. **115**:867, 1973), destroying these lesions as if cautery had been used (Comparison of cautery and acid powder in benign cervical lesions, Southwest. Med. J. 50:111, 1969).

An Ultra-Scientific electronic pH recorder determines the acidity and alkalinity of the vagina and cervix any time that the small, fine tips touch the cervix. We have recorded the pH in more than 5,000 cervical ectropions, ulcers, dysplasias, and carcinomas in situ. Every dysplastic cervix was on the alkaline pH side of the scale. In over 15,000 vaginas which had acidity or pH values in the normal vaginal range of 3.0 to 3.5 to 4.2, not one case of cervical dysplasia has been found. Coppleson and Reid, in their textbook, *Pre-Cancer Cervical Lesions,* also reported electronic pH recordings of dysplastic cervical lesions. Under their study of the "Nature of the Stimulus to Produce Metaplasia," they mentioned the suggestion of Carmichael and Jeaffreson who stated that some "vaginal factor may be the cause" and Walz who thought that a pH vaginal variation could be a cause or the cause. There are very few sites in the body where the pH range or variation are as great as in the cervix. Coppleson and Reid observed columnar mucus-secreting cells at a pH above 7.4 while below this pH only squamous epithelial cells or normal vaginal cells were seen. The acid pH range acts on the columnar cell lysosomes, causing their breakdown and release of the 36 lysosomal enzymes which destroy dysplastic cells and those of carcinoma in situ. Alkaline and weakly acid pH levels favor growth of these abnormal cells and finally lead to invasive cancer. The pH variations may have other effects, as Coppleson and Reid mentioned, such as profound effects on a variety of biochemical synthesis and energy production systems of cells, by influencing the optimal "working conditions" of the enzymes concerned. Acidity and alkalinity have been observed to play a very important part in the development of dysplasia, carcinoma in situ, and invasive cervical cancer. We have verified this in studying hydrogen and hydroxyl ions of the cervix for over 35 years with an electronic pH recorder. All cases of cervical dysplasia, carcinoma in situ, and invasive cancer have had an alkaline recording.

It is believed by our group that it is the hydrogen ion which maintains the cervix in its normal, healthy condition. Up to now, we had no way to bring about and maintain the acidity of the cervix in the normal pH range of 3.0 to 3.5 to 4.2. This has been accomplished in the Obstetrical and Gynecological Research Institute over the past 40 years. "Micronized or finely pulverized aluminum powder"* is made so that it will maintain the cervix in its healthy condition, and all dysplasia and carcinoma in situ will be destroyed. If the powder is used instead of douches and after coitus or weekly in the sexually active woman, there will be no dysplasia or carcinoma in situ; cervical cancer can be reduced by as much as 95%.

Which patients should have cervical cauterization? Any woman who has had a baby and is aged 40 or more should undergo cervical cauterization. The large majority of women who have had babies do have some lesions of the cervix, due to a cervical tear. Cooke's "whole-erosion" cauterization is done. Streak cauterization is no longer used because of fibrous formation in the cut streaks. The whole cervical surface is cauterized until it is white like coagulated egg white. One cannot harm the cervix by cautery but dysplasia can develop if it is not carried out.

Any woman with a cervical lesion must undergo Lugol's staining and biopsy of the white areas. The whole area is whitened, with treatment of even that part of the cervix which does not have some ectropionic tissue.

In 1948, in my textbook, *Practical Office Gynecology,* I reported that packing the normal vagina and cervix with hydroxyl ions produced cervical ulcers and ectropions and adenosis, as seen in young women whose mothers received diethylstilbestrol during pregnancy. The ectropions even grew over the vaginal walls. Then normal physiologic vaginal acid powder was instilled in the vagina and the vaginal and cervical ulcers atrophied. We have so many cervical lesions today that we do not have enough time or physicians to treat them, so we began to use the "hydrogen" or "micronized or pulverized aluminum powder," which, when instilled by the patient or by the physician, produces a vaginal acidity in the normal physiologic acid pH range of 3.0 to 4.2. In this pH range there will be no dysplasia or carcinoma in situ. The patient can instill this powder any time that she wishes or feels that the vagina is not "clean," after coitus, or instead of douches. If the woman is sexually active it should be used twice weekly. The powder destroys not only dysplasia and carcinoma in situ but also *Trichomonas vaginalis, Candida albicans, Hemophilus vaginalis,* and all fungi, molds, and yeasts. One treatment will eliminate vaginitis and cervicitis from the practice of medicine and use of this powder after coitus and instead of douching will prevent these pathogens from reinfecting the vagina.

*Micronized aluminum powder can be obtained at any chemical supply house or in package form from Oakdale Laboratory, 1101 Oakdale Laboratory, 1101 Oakdale, Houston, Texas 77004.

In the article by Kauraniemi and associates, the risk of malignant or premalignant lesions was lower than in the rest of the population. They believe that the cautery and we believe the hydrogen ions destroyed the atypical epithelium at some stage of the natural progression of the disease. They also stated that even if it is impossible to prove cauterization of benign cervical lesions is the reason for the reduction of cervical cancer, the treatment should be seriously considered as a means of preventing cervical cancer.

In our gynecology clinics we think the most important procedures in gynecology are cauterization, conization, coagulation, and cryocauterization of benign cervical lesions.

Now with this powder the patient can destroy all benign cervical lesions. This powder is prescribed in all sexually active women, instead of water-made douches, so that any dysplastic lesion or carcinoma in situ will not become malignant and will revert back into normal vaginal cells. The acid environment has definitely been shown to cause endocervical cells to remain high in the cervical canal where they normally thrive in the alkaline environment, thereby maintaining the cervix free of dysplasia and carcinoma in situ and, in so doing, preventing the development of cervical cancer.

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Fetal heart rate response to amniocentesis

To the Editors:

I read with interest the article, "Fetal heart rate reaction to amniocentesis as an indicator of fetal well-being" by John T. Harrison, M.D., F.A.C.O.G., and Joseph F. Marino, D.O., in the JOURNAL (132:49, 1978). I wish to add to their interesting findings our own experience of a study of 107 amniocenteses under continuous fetal heart rate (FHR) monitoring which was published in 1976[1] and since then has grown to 250 cases, being a routine procedure in our Department for assessment of fetal well-being in any case in which amniocentesis is indicated.

The two typical patterns of reaction, namely, tachycardia and bradycardia, correspond well with the findings of Harrison and Marino.[1, 2] There are, however, two points which should be clarified according to our experience. As the "normal" response of the fetus to the stimulus of amniocentesis is tachycardia (82.2% in our first series) "no response" or an "equivocal" response should be regarded as a sign of the existence of some degree of fetal jeopardy (proved in 42.2% of the cases of our first series), and sometimes as an indication of severe distress as in these cases which show a response of bradycardia.[2] Therefore, those cases in which an "equivocal" response is found need close observation and evaluation by additional methods, such as an oxytocin challenge test and a fetal nonstress reactive test.

In cases in which fetal bradycardia follows amniocentesis, maternal hypotension due to a maternal "vasovagal" reflex should be ruled out as the cause of fetal bradycardia.[3] Maternal "vasovagal" reflex can be observed clinically during the procedure. Another helpful point in recognizing this apparently harmless and transient cause of fetal bradycardia is a "normal" acceleration which precedes the bradycardia. By recognizing this cause of fetal bradycardia (which occurred in 6.6% of our second series) false positive results can be minimized.

We fully agree with the authors that in any amniocentesis procedure continuous FHR monitoring can contribute additional valuable information, as suggested by us in 1974.[4, 5]

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Perinatal mortality rate associated with diabetic pregnancy

To the Editors:

In their stimulating article entitled "Diabetic pregnancy and perinatal morbidity," published in the "Current Developments" section in THE JOURNAL (131:560, 1978), Kitzmiller and associates have provided a wealth of information helpful to any endocrinologist caring for pregnant diabetic patients. However, one finds it difficult to accept that the perinatal mortality rate was 3.4%, particularly when the authors deleted seven patients who underwent elective abortions (4%), including three women (2%) in whom pregnancy was terminated after antenatal diagnosis of fetal anencephaly. Their delection cannot be justified since these patients were registered with the pregnancy clinic of the Joslin Foundation and must have been provided the same kind of antenatal care as the others received. Apparently the authors deleted this group of patients to achieve an impressive perinatal mortality figure of

3.4%. If one includes this group of patients for purposes of calculating the perinatal mortality rate, the true figures would be 5.4%, which is still impressive but takes away the claim of best figures from the authors, since a rate of 5% or less has been already reported by various centers.[1]

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REFERENCE

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Reply to Dr. Khardori

To the Editors:

In the closing paragraph of our article, we tried to emphasize the many factors which play a role in improved perinatal survival in pregnancies attaining a stage of viability in women with insulin-dependent diabetes. We cited a high proportion of cooperative, well-motivated patients, a low incidence of pyelonephritis and pre-eclampsia, application of measures that can assess fetal well-being, prediction of fetal pulmonary maturity by amniotic fluid analysis, and advances in neonatal care. We also stated that "the availability of the α-fetoprotein assay and ultrasonography has allowed the early diagnosis of anencephaly so that pregnancies may be terminated." This is an example of the application of new medical technology to reduce the incidence of severely abnormal infants delivered after 24 weeks' gestation. We also would not include pregnancies aborted due to the diagnosis of Down's syndrome in our perinatal mortality figures—they would be considered in our abortion statistics.

On the other hand, we completely agree with Dr. Khardori that congenital anomalies are a very important outcome variable to consider when assessing management of diabetic patients before pregnancy and in early pregnancy. For this reason, our three cases of anencephaly were included in our incidence of 9% major congenital anomalies. In the article, we emphasized that the relationship of the metabolic perturbations of maternal diabetes to birth defects in the offspring is a very important area for research.

Finally, I believe it is demeaning and trivial to claim the best record for anything in this complicated and changing world. In the paper we stated that "the perinatal mortality rate in this [1975 to 1976] series (34/1,000) is among the best reported to date for large groups of women with severe diabetes." Over the four years, 1975 to 1978, our perinatal mortality rate for 270 diabetic women was 36/1,000.

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Prior immunization by herpesvirus

To the Editors:

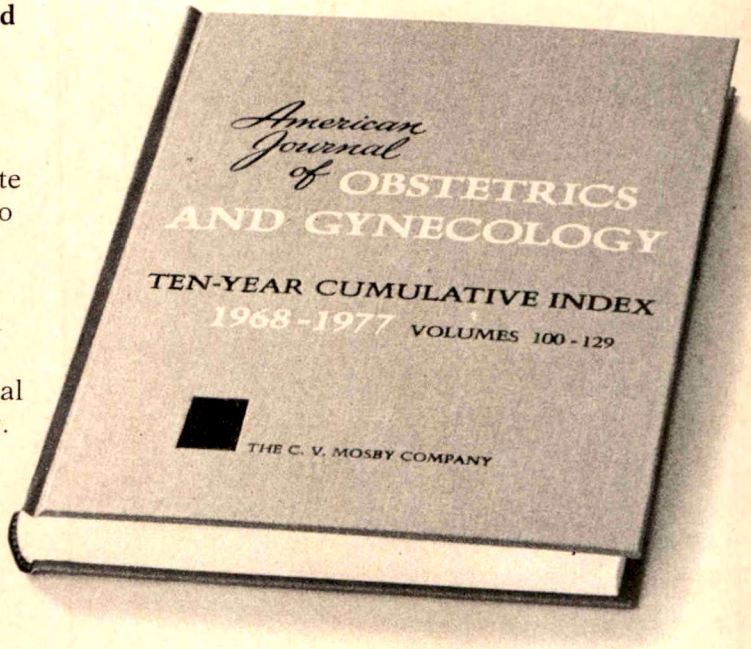
In their article concerning the effects of prior immunization by herpesvirus type 1, Asher and his coworkers were not able to demonstrate protection from challenge with herpesvirus type 2 (AM. J. OBSTET. GYNECOL. 131:788, 1978). They attributed this to possible strain difference among type 2 virus.

As reported previously (AM. J. OBSTET. GYNECOL. 125:41, 1976), we *were* able to demonstrate protection of newborn mice from lethal infection due to maternal vaginal challenge with type 2 herpesvirus after maternal immunization with type 1 virus. Perhaps this is an example of strain differences suggested by the authors. I would encourage them to continue with their model of latent infection to test this hypothesis.

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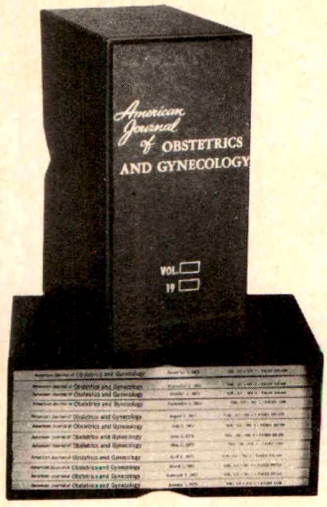
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Note: Tumorigenicity Studies in Rodents. Metronidazole has shown evidence of tumorigenic activity in a number of studies involving chronic, oral administration in mice and rats.

Most prominent among the effects in the mouse was the promotion of pulmonary tumorigenesis. This has been observed in all five reported studies in that species, including one study in which the animals were dosed on an intermittent schedule (administration during every fourth week only). The published results of one of the mouse studies indicate increases in the incidence of malignant lymphomas as well as pulmonary neoplasms associated with lifetime feeding of the drug. All these effects are statistically significant.

Two long-term toxicity studies in the rat have been completed. There was a statistically significant increase in the incidence of various neoplasms, particularly mammary tumors, among female rats administered metronidazole over that noted in the concurrent female control groups.

Two lifetime tumorigenicity studies in hamsters have been performed and reported to be negative.

Metronidazole has been reported to potentiate the anticoagulant effect of coumarin and warfarin resulting in a prolongation of prothrombin time. This possible drug interaction should be considered when Flagyl is prescribed for patients on this type of anticoagulant therapy.

Precautions: Mild leukopenia has been reported during Flagyl use; total and differential leukocyte counts are recommended before and after treatment with the drug, especially if a second course is necessary. Avoid alcoholic beverages during Flagyl therapy because abdominal cramps, nausea, vomiting, headaches and flushing may occur. Discontinue Flagyl promptly if abnormal neurologic signs occur. Exacerbation of moniliasis may occur. In amebic liver abscess, aspirate pus during metronidazole therapy.

Adverse Reactions: Nausea, headache, anorexia, vomiting, diarrhea, epigastric distress, abdominal cramping, constipation, a metallic, sharp and unpleasant taste, furry tongue, glossitis and stomatitis possibly associated with a sudden overgrowth of *Candida*, exacerbation of vaginal candidiasis, an occasional reversible moderate leukopenia, dizziness, incoordination and ataxia, numbness or paresthesia of an extremity, fleeting joint pains, confusion, irritability, depression, insomnia, mild erythematous eruptions, "weakness," urticaria, flushing, nasal congestion, dryness of the mouth, vagina or vulva, pruritus, dysuria, cystitis, a sense of pelvic pressure, dyspareunia, fever, polyuria, incontinence, decrease of libido, proctitis, pyuria and darkened urine have occurred in patients receiving the drug. Patients receiving Flagyl may experience abdominal distress, nausea, vomiting, flushing or headache if alcoholic beverages are consumed. The taste of alcoholic beverages may also be modified. Flattening of the T-wave may be seen in ECG tracings.

Dosage and Administration: ***For Trichomoniasis:*** The recommended dosage for both male and female is one 250-mg. tablet orally three times daily for seven days. When repeat courses of the drug are required, it is recommended that an interval of 4 to 6 weeks elapse between courses and that the presence of the trichomonad be reconfirmed by appropriate laboratory measures. Total and differential leukocyte counts should be made before, during and after retreatment. The male consort should be treated in any event in cases of reinfection.

For Amebiasis: *Adults:* For acute intestinal amebiasis, 750 mg. orally three times daily for 5 to 10 days.

For amebic liver abscess: *Adults:* 500 mg. or 750 mg. orally three times daily for 5 to 10 days.

Children: 35 to 50 mg./kg. of body weight/24 hours, divided into three doses, orally for 10 days.

SEARLE **Searle & Co.**
San Juan, Puerto Rico 00936

Address medical inquiries to:
G. D. Searle & Co.
Medical Communications Department, Box 5110
Chicago, Illinois 60680



His trichomoniasis can make her therapy useless unless they both take..

When the male is not treated for *Trichomonas vaginalis,* the female—no matter how well she cooperates with therapy—probably will become reinfected. To arrest this infection/reinfection cycle, both infected partners must be treated simultaneously.

The only systemic trichomonacide—In the female, trichomoniasis is a multiorgan disease. Trichomonads invade the vagina, and are often deeply entrenched in the endocervix, Skene's and Bartholin's glands, the urethra, and the bladder. The male genitourinary tract has seven possible sites of infection. Only the systemic action of Flagyl can eliminate sequestered trichomonads from these sites; topical treatments are ineffective.

Effective in both partners—Because it reaches infection sites via the bloodstream, Flagyl is the only trichomonacide that is effective in both men and women. And Flagyl is the only available agent of its kind.

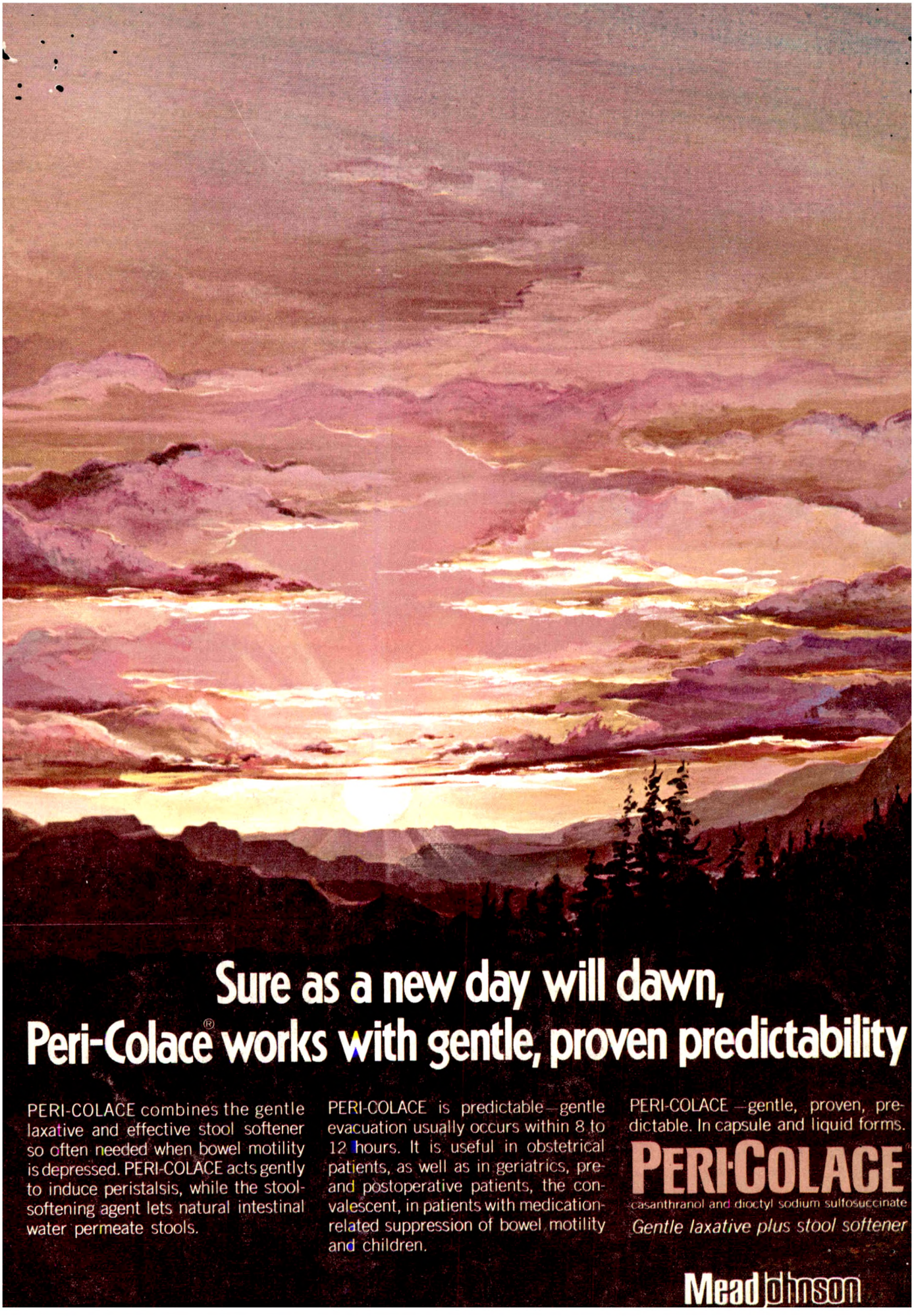
The only effective trichomonacide for couples

Flagyl® 250-mg. tablets (metronidazole)

Please see adjacent page for brief summary of prescribing information.

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Sure as a new day will dawn, Peri-Colace® works with gentle, proven predictability

PERI-COLACE combines the gentle laxative and effective stool softener so often needed when bowel motility is depressed. PERI-COLACE acts gently to induce peristalsis, while the stool-softening agent lets natural intestinal water permeate stools.

PERI-COLACE is predictable—gentle evacuation usually occurs within 8 to 12 hours. It is useful in obstetrical patients, as well as in geriatrics, pre- and postoperative patients, the convalescent, in patients with medication-related suppression of bowel motility and children.

PERI-COLACE—gentle, proven, predictable. In capsule and liquid forms.

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casanthranol and dioctyl sodium sulfosuccinate

Gentle laxative plus stool softener

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Why the choice is Cu-7®

intrauterine copper contraceptive









1. She wants nonhormonal contraception.
2. She wants to space her family.
3. She smokes.
4. She has passed the "Pill" years.

Freedom—intrauterine contraception is the most convenient of all contraceptive methods.

Comfort—smallest inserter diameter of all IUDs. This means minimal discomfort during insertion.

Cu-7	Lippes Loop® D	Saf-T-Coil® (Nullip)	Saf-T-Coil® (Standard)
3.07 mm.	5.33 mm.	3.76 mm.	4.50 mm.

Security—high efficacy and relatively low incidence of expulsion and medical removal.

(Rates—based on labeling claims—expressed as events per 100 women through 12 months of use for parous women)*	Cu-7[1]	Lippes Loop D[2]	Saf-T-Coil
Pregnancy	1.9	2.7	2.4
Expulsion	5.7	12.7	18.3
Medical Removal	10.9	15.2	15.6

*These rates are derived from separate studies conducted by different investigators in several population groups. Different rates have been reported from other clinical trials.

References: 1. Data on file at Searle Laboratories. 2. Physicians' Desk Reference, Medical Economics Company, Oradell, N.J., 1978, pp. 1216, 1521.

Intrauterine contraception is not appropriate for all women. Please see complete product information prior to use. A brief summary of product information appears on the next page.

Description: The plastic component of the Cu-7 is composed of pharmaceutical grade polypropylene homopolymer with barium sulfate added to render it radiopaque. Its shape approximates the number 7. It is substantially smaller than previously available intrauterine devices; the vertical dimension measures 36 mm. and the horizontal, 26 mm.

Coiled around the vertical limb is a pure, virgin electrolytic copper wire providing approximately 200mm^2 of exposed copper surface area. A retrieval thread is fastened to the free end of the vertical limb of the Cu-7.

The Cu-7 is supplied with a simple tubular polypropylene inserter. All components are sterile.

Mode of Action: Available data indicate that the contraceptive effectiveness of the Cu-7 is enhanced by a minute quantity of copper released continuously from the coiled copper into the uterine cavity.

The exact mechanism by which metallic copper enhances the contraceptive effect of an IUD has not been conclusively demonstrated. Various hypotheses have been advanced, the most common being that copper placed in the uterus interferes with enzymatic or other processes that regulate blastocyst implantation.

Animal studies suggest that copper may play an additional role by reduction of sperm transport within the uterine environment.

Indication and Usage: The Cu-7 is indicated for contraception.

Contraindications: The Cu-7 should not be inserted when any of the following conditions exist: pregnancy or suspicion of pregnancy; abnormalities of the uterus resulting in distortion of the uterine cavity; acute pelvic inflammatory disease or a history of repeated pelvic inflammatory disease; postpartum endometritis or infected abortion in the past three months; known or suspected uterine or cervical disease such as hyperplasia or carcinoma including unresolved, abnormal "Pap" smear; vaginal bleeding of unknown etiology; untreated acute cervicitis until infection is controlled; diagnosed Wilson's disease; known or suspected allergy to copper; previous ectopic pregnancy, and significant anemia.

Warnings

1. Pregnancy: (a) Long-term effects. The long-term effects on the offspring of the presence of copper in the uterus when pregnancy occurs with the Cu-7 are unknown.

(b) Septic abortion. Reports have indicated an increased incidence of septic abortion associated in some instances with septicemia, septic shock and death in patients becoming pregnant with an IUD in place. Most of these reports have been associated with the mid-trimester of pregnancy. In some cases, the initial symptoms have been insidious and not easily recognized. If pregnancy should occur with a Cu-7 in situ, the Cu-7 should be removed if the thread is visible or, if removal proves to be or would be difficult, interruption of the pregnancy should be considered and offered to the patient as an option, bearing in mind that the risks associated with an elective abortion increase with gestational age.

(c) Continuation of pregnancy. If the patient chooses to continue the pregnancy and the Cu-7 remains in situ, she must be warned of the increased risk of spontaneous abortion and the increased risk of sepsis, including death. The patient must be closely observed and she must be advised to report immediately all abnormal symptoms, such as flu-like syndrome, fever, abdominal cramping and pain, bleeding, or vaginal discharge, because generalized symptoms of septicemia may be insidious.

2. Ectopic pregnancy: (a) A pregnancy which occurs with an IUD in situ is more likely to be ectopic than a pregnancy occurring without an IUD. Therefore, patients who become pregnant while using a Cu-7 should be carefully evaluated for the possibility of an ectopic pregnancy.

(b) Special attention should be directed to patients with delayed menses, slight metrorrhagia and/or unilateral pelvic pain, and to those patients who wish to interrupt a pregnancy occurring in the presence of a Cu-7, to determine whether ectopic pregnancy has occurred.

3. Pelvic infection: An increased risk of pelvic inflammatory disease associated with the use of IUDs has been reported. While unconfirmed, this risk appears to be greatest for young women who are nulliparous and/or who have a multiplicity of sexual partners. Salpingitis can result in tubal damage and occlusion, thereby threatening future fertility. Therefore, it is recommended that patients be taught to look for symptoms of pelvic inflammatory disease. The decision to use an IUD in a particular case must be made by the physician and patient with the consideration of a possible deleterious effect on future fertility.

Pelvic infection may occur with a Cu-7 in situ and at times result in the development of tubo-ovarian abscesses or general peritonitis. The symptoms of pelvic infection include: new development of menstrual disorders (prolonged or heavy bleeding), abnormal vaginal discharge, abdominal or pelvic pain, dyspareunia, fever. The symptoms are especially significant if they occur following the first two or three cycles after insertion. Appropriate aerobic and anaerobic bacteriologic studies should be done and antibiotic therapy initiated promptly. If the infection does not show marked clinical improvement within 24 to 48 hours, the Cu-7 should be removed and the continuing treatment reassessed on the basis of the results of culture and sensitivity tests.

4. Embedment: Partial penetration or lodging of the Cu-7 in the endometrium or myometrium can result in a difficult removal. This may occur more frequently in smaller uteri. (See removal instructions.)

5. Perforation: Partial or total perforation of the uterine wall or cervix may occur with the use of the Cu-7, usually during insertions into patients sooner than two months after abortion or delivery or in uterine cavities too small for the Cu-7. The possibility of perforation must be kept in mind during insertion and at the time of any subsequent examination. If perforation occurs, laparotomy or laparoscopy should be performed as soon as medically feasible and the Cu-7 removed. Abdominal adhesions, intestinal penetration, intestinal obstruction, and local inflammatory reaction with abscess formation and erosion of adjacent viscera may result if the Cu-7 is left in the peritoneal cavity.

6. Medical diathermy: The use of medical diathermy (short-wave and microwave) in a patient with a metal-containing IUD may cause heat injury to the surrounding tissue. Therefore, medical diathermy to the abdominal and sacral areas should not be used on patients using a Cu-7.

7. Effects of copper: Additional amounts of copper available to the body from the Cu-7 may precipitate symptoms in women with undiagnosed Wilson's disease. The incidence of Wilson's disease is 1 in 200,000.

Precautions

1. Patient counseling: Prior to the insertion the physician, nurse, or other trained health professional must provide the patient with the Patient Brochure. The patient should be given the opportunity to read the brochure and discuss fully any questions she may have concerning the Cu-7 as well as other methods of contraception.

2. Patient evaluation and clinical considerations: a) A complete medical history should be obtained to determine conditions that might influence the selection of an IUD. A physical examination should include a pelvic examination, "Pap" smear, gonorrhea culture and, if indicated, appropriate tests for other forms of venereal disease. The physician should determine that the patient is not pregnant.

(b) The uterus should be carefully sounded prior to the insertion to determine the degree of patency of the endocervical canal and the internal os, and the direction and depth of the uterine cavity. Exercise care to avoid perforation with the sound. DO NOT USE THE Cu-7 INSERTION INSTRUMENT AS A SOUND. In occasional cases, severe cervical stenosis may be encountered. Do not use excessive force to overcome this resistance.

(c) The uterus usually sounds to a depth of 6 to 8 cm. Insertion of a Cu-7 into a uterine cavity measuring less than 6.5 cm. by sounding may increase the incidence of pain, bleeding, partial or complete expulsion, perforation, and possibly pregnancy.

(d) To reduce the possibility of insertion in the presence of an existing undetermined pregnancy, the optimal time for insertion is the latter part of the menstrual flow or one or two days thereafter. The Cu-7 should not be inserted post partum or post abortion until involution of the uterus is complete. The incidence of perforation and expulsion is greater if involution is not complete.

It is, however, necessary to place the Cu-7 as high as possible within the uterine cavity to help avoid partial or complete expulsion that could result in pregnancy.

Since the Cu-7 represents a different design in intrauterine contraception, physicians are cautioned that it is imperative for them to become thoroughly familiar with the instructions for use before attempting placement of the Cu-7.

(e) IUDs should be used with caution in those patients who have an anemia or a history of menorrhagia or hypermenorrhea. Patients experiencing menorrhagia and/or metrorrhagia following IUD insertion may be at risk for the development of hypochromic microcytic anemia. Also, IUDs should be used with

(f) Syncope, bradycardia or other neurovascular episodes may occur during insertion or removal of IUDs, especially in patients with a previous disposition to these conditions.

(g) Patients with valvular or congenital heart disease are more prone to develop subacute bacterial endocarditis than patients who do not have valvular or congenital heart disease. Use of an IUD in these patients may represent a potential source of septic emboli.

(h) Use of an IUD in those patients with acute cervicitis should be postponed until proper treatment has cleared up the infection.

(i) Since the Cu-7 may be partially or completely expelled, patients should be reexamined and evaluated shortly after the first postinsertion menses, but definitely within three months after insertion. Thereafter annual examination with appropriate medical and laboratory evaluation should be carried out. The Cu-7 should be replaced every three years.

(j) The patient should be told that some bleeding or cramps may occur during the first few weeks after insertion, but if these symptoms continue or are severe she should report them to her physician. She should be instructed on how to check after each menstrual period to make certain that the thread still protrudes from the cervix and cautioned that there is no contraceptive protection if the Cu-7 has been expelled. She should also be cautioned not to dislodge the Cu-7 by pulling on the thread. If a partial expulsion occurs, removal is indicated and a new Cu-7 may be inserted. The patient should be told to return within three years for removal of the Cu-7 and for replacement if desired.

(k) A copper-induced urticarial allergic skin reaction may develop in women using a copper-containing IUD. If symptoms of such an allergic response occur, the patient should be instructed to tell the consulting physician that a copper-containing device is being used.

(l) The Cu-7 should be removed for the following medical reasons: menorrhagia and/or metrorrhagia producing significant anemia; uncontrolled pelvic infection; intractable pain often aggravated by intercourse, dyspareunia; pregnancy, if the thread is visible; endometrial or cervical malignancy; uterine or cervical perforation; or any indication of partial expulsion.

(m) If the retrieval thread cannot be visualized it may have retracted into the uterus or have been broken off, or the Cu-7 may have been expelled. Localization usually may be made by feeling with a probe; if not, x-ray or sonography can be used. When the physician elects to recover a Cu-7 with the thread not visible, the removal instructions should be considered.

(n) If any patient with a Cu-7 suddenly develops overt clinical hepatitis or abnormal liver function tests, appropriate diagnostic procedures should be initiated.

Adverse Reactions: Perforations of uterus and cervix have occured. Perforation into the abdomen has been followed by abdominal adhesions, intestinal penetration, intestinal obstruction, local inflammatory reaction with abscess formation and erosion of adjacent viscera. Pregnancy has occurred with the Cu-7 in situ and when the Cu-7 has been partially or completely expelled.

The incidence of spontaneous abortion, when conception occurs with intrauterine devices in situ, appears to be increased over that in unprotected women. Insertion cramping, usually of no more than a few seconds duration, may occur; however, some women may experience residual cramping for several hours or even days. Intermenstrual spotting or bleeding or prolonged or increased menstrual flow may occur.

Pelvic infection including salpingitis with tubal damage or occlusion has been reported. This may result in future infertility. Complete or partial expulsion of the Cu-7 may sometimes occur, particularly in those patients with uteri measuring less than 6.5 cm. by sounding. Urticarial allergic skin reaction may occur. The following complaints have also been reported with IUDs although their relation to the Cu-7 has not been established: amenorrhea or delayed menses, backaches, cervical erosion, cystic masses in the pelvis, vaginitis, leg pain or soreness, weight loss or gain, nervousness, dyspareunia, cystitis, endometritis, septic abortion, septicemia, leukorrhea, ectopic pregnancy, difficult removal, uterine embedment, anemia, pain, neurovascular episodes including bradycardia and syncope secondary to insertion, dysmenorrhea, and fragmentation of the IUD.

Directions for Use: The Cu-7 is to be placed within the uterine cavity. See the Procedure for Insertion for two insertion techniques.

The small diameter of the Cu-7 facilitates easy insertion in nulligravidous and nulliparous, as well as parous women. The optimal time of insertion is during the latter part of the menstrual flow or one or two days thereafter. The cervical canal is relatively more patent at this time, and there is little chance that the patient may be pregnant.

Present information indicates that efficacy is retained for 36 months. There is no evidence that contraceptive efficacy decreases with time up to three years of use, but until adequate data indicating a longer effective life become available, the Cu-7 must be removed within 36 months from the date of insertion and a new one inserted if desired. If partial expulsion occurs, removal is indicated, and a new Cu-7 may be inserted. Removal of the Cu-7 may also be indicated in the event of heavy or persistent bleeding.

The physician should become thoroughly familiar with the instructions for use before attempting insertion or removal of the Cu-7.

Clinical Efficacy: In clinical trials of the Cu-7 conducted by Searle Laboratories, use effectiveness was determined as follows for parous and nulliparous women, as tabulated by the life table method. (Rates are expressed as cumulative events per 100 women through 12, 24, and 36 months of use.)

This experience encompasses 387,131 woman-months of use, including 12 months for 11,517 women, 24 months for 7,895, and 36 months for 3,661.

	12 Months		24 Months		36 Months	
	Parous	Nulliparous	Parous	Nulliparous	Parous	Nulliparous
Pregnancy	1.9	1.7	2.9	2.6	3.4	3.4

How Supplied

Available in cartons of 6, 30 and 100 sterile units (Cu-7 with an inserter) and sufficient patient leaflets and identification cards.

Please see complete product labeling for additional information, including insertion and removal instructions.

SEARLE **Searle Laboratories**
Division of Searle Pharmaceuticals Inc.
Box 5110, Chicago, Illinois 60680

Cu-7® intrauterine copper contraceptive

—the leading IUD



A lot less than everyone once thought. Just a few years ago, a 50-mcg dosage was considered low. Today, there's an effective combination oral contraceptive containing 30 mcg of estrogen: Loestrin 1.5/30.

In spite of a 40% reduction in the dose of estrogen, efficacy of Loestrin 1.5/30 is considered comparable to that of combination oral contraceptives containing higher levels of estrogen.

Irregular bleeding is somewhat more frequent with Loestrin 1.5/30 than with combinations containing larger doses of estrogen. With continued use, however, the frequency decreases.

And if you're concerned about your patients' intake of estrogen over an extended period of time, Loestrin 1.5/30 contains 30 mcg of ethinyl estradiol, so patient exposure to estrogen is reduced.

LOESTRIN® 1.5/30

(1.5 mg norethindrone acetate and
30 mcg ethinyl estradiol tablets, USP)

a 30-mcg alternative to higher estrogen

ualization of
nmalian ovulation.
pyright © 1971, by
e-Science Co., Ltd.,
an.

See opposite page for prescribing information

Brief Summary of Prescribing Information
LOESTRIN® 1.5/30
(1.5 mg norethindrone acetate and 30 mcg ethinyl estradiol tablets, USP) See section under Special Notes on Administration and How Supplied.

DESCRIPTION
Loestrin 1.5/30 Products are progestogen-estrogen combinations.

INDICATION AND USAGE
Loestrin 1.5/30 Products are indicated for the prevention of pregnancy in women who elect to use oral contraceptives.

In clinical trials with Loestrin 1.5/30 involving 17,139 therapy cycles, there was a pregnancy rate of 0.49 per 100 woman years.

Dose-related risk of thromboembolism from oral contraceptives: Studies have shown a positive association between the dose of estrogens in oral contraceptives and the risk of thromboembolism. It is prudent and in keeping with good principles of therapeutics to minimize exposure to estrogen. The oral contraceptive prescribed for any given patient should be that product which contains the least amount of estrogen that is compatible with an acceptable pregnancy rate and patient acceptance.

CONTRAINDICATIONS
1. Thrombophlebitis or thromboembolic disorders
2. A past history of deep-vein thrombophlebitis or thromboembolic disorders
3. Cerebral vascular or coronary artery disease
4. Known or suspected carcinoma of the breast
5. Known or suspected estrogen-dependent neoplasia
6. Undiagnosed abnormal genital bleeding
7. Known or suspected pregnancy (See No. 5 under WARNINGS.)

WARNINGS

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

The use of oral contraceptives is associated with increased risk of several serious conditions including thromboembolism, stroke, myocardial infarction, hepatic adenoma, gallbladder disease, and hypertension. Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks.

1. *Thromboembolic Disorders and Other Vascular Problems:* An increased risk of thromboembolic and thrombotic disease associated with the use of oral contraceptives is well-established. Studies have demonstrated an increased risk of fatal and nonfatal venous thromboembolism and stroke, both hemorrhagic and thrombotic.

Cerebrovascular disorders: In a collaborative study in women with and without predisposing causes, it was estimated that the risk of hemorrhagic stroke was 2.0 times greater in users than nonusers, and the risk of thrombotic stroke was 4.0 to 9.5 times greater.

Myocardial infarction: An increased risk of myocardial infarction associated with oral contraceptives has been reported confirming a previously suspected association. These studies found that the greater the number of underlying risk factors (cigarette smoking, hypertension, hypercholesterolemia, obesity, diabetes, history of preeclamptic toxemia) for coronary artery disease, the higher the risk of developing myocardial infarction, regardless of whether the patient was an oral contraceptive user or not. Oral contraceptives, however, were found to be a clear additional risk factor.

It has been estimated that users who do not smoke (smoking is considered a major predisposing condition to myocardial infarction) are about twice as likely to have a fatal myocardial infarction as nonusers who do not smoke. Oral contraceptive users who are smokers have about a fivefold increased risk of fatal infarction compared to users who do not smoke, but about a tenfold to twelvefold increased risk compared to nonusers who do not smoke. The amount of smoking is also an important factor.

Risk of dose: In an analysis of data, British investigators concluded that the risk of thromboembolism including coronary thrombosis is directly related to the dose of estrogen used in oral contraceptives; however, the quantity of estrogen may not be the sole factor involved.

Estimate of excess mortality from circulatory diseases: The risk of diseases of the circulatory system is concentrated in older women, in those with a long duration of use, and in cigarette smokers.

A study of available data from a variety of sources concluded that the mortality associated with all methods of birth control is low and below that associated with childbirth, with the exception of oral contraceptives in women over 40 who smoke.

The risk of thromboembolic and thrombotic diseases associated with oral contraceptives increases with age after approximately age 30 and, for myocardial infarction, is further increased by hypertension, hypercholesterolemia, obesity, diabetes, or history of preeclamptic toxemia, and especially by cigarette smoking.

The physician and the patient should be alert to the earliest manifestations of thromboembolic and thrombotic disorders. Should any occur or be suspected, the drug should be discontinued immediately.

A fourfold to sixfold increased risk of postsurgery thromboembolic complications has been reported in users. If feasible, oral contraceptives should be discontinued at least four weeks before surgery of a type associated with an increased risk of thromboembolism or prolonged immobilization.

2. *Ocular lesions:* Neuro-ocular lesions, such as optic neuritis or retinal thrombosis, have been associated with the use of oral contraceptives. Discontinue the oral contraceptive if there is unexplained sudden or gradual, partial, or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal vascular lesions.

3. *Carcinoma:* Long-term continuous administration of estrogen in certain animal species increases the frequency of carcinoma of the breast, cervix, vagina, and liver.

In humans, an increased risk of endometrial carcinoma associated with the prolonged use of exogenous estrogen in postmenopausal women has been reported. However, there is no evidence suggesting increased risk of endometrial cancer in users of conventional combination or progestogen-only oral contraceptives.

Studies found no evidence of increase in breast cancer in women taking oral contraceptives; however, an excess risk in users with documented benign breast disease was reported.

There is no confirmed evidence of an increased risk of cancer associated with oral contraceptives. Close clinical surveillance of users is, nevertheless, essential. In cases of undiagnosed persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be taken to rule out malignancy. Women with a strong family history of breast cancer, or who have breast nodules, fibrocystic disease, or abnormal mammograms, should be monitored with particular care.

4. *Hepatic Tumors:* Benign hepatic adenomas have been found to be associated with oral contraceptives. Because hepatic adenomas may rupture and may cause death through intra-abdominal hemorrhage, they should be considered in women presenting abdominal pain and tenderness, abdominal mass, or shock.

A few cases of hepatocellular carcinoma have been reported in women taking oral contraceptives. The relationship of these drugs to this type of malignancy is not known at this time.

5. *Usage in or Immediately Preceding Pregnancy; Birth Defects in Offspring, and Malignancy in Female Offspring:* During early pregnancy, female sex hormones may seriously damage the offspring.

An increased risk of congenital anomalies, including heart defects and limb defects, has been reported with the use of oral contraceptives in pregnancy.

There is some evidence that triploidy and possibly other types of polyploidy are increased among abortuses from women who become pregnant soon after ceasing oral contraceptives.

Pregnancy should be ruled out before continuing an oral contraceptive in any patient who has missed two consecutive menstrual periods. If the patient has not adhered to the schedule, the possibility of pregnancy should be considered at the time of the first missed period, and oral contraceptives should be withheld until pregnancy has been ruled out. If pregnancy is confirmed, the patient should be apprised of the potential risks to the fetus and the advisability of continuation of the pregnancy should be discussed.

Women who discontinue oral contraceptives with the intent of becoming pregnant should use an alternate form of contraception for a period of time before attempting to conceive.

Administration of progestogen-only or progestogen-estrogen combinations to induce withdrawal bleeding should not be used as a test of pregnancy.

6. *Gallbladder Disease:* Studies report an increased risk of surgically confirmed gallbladder disease in users of oral contraceptives.

7. *Carbohydrate and Lipid Metabolic Effects:* Because decreased glucose tolerance has been observed in a significant percentage of patients, prediabetic and diabetic patients should be carefully observed while receiving oral contraceptives.

An increase in triglycerides and total phospholipids has been observed.

8. *Elevated Blood Pressure:* An increase in blood pressure has been reported in patients receiving oral contraceptives. The prevalence in users increases with longer exposure. Age is also strongly correlated with development of hypertension. Women who previously have had hypertension during pregnancy may be more likely to develop elevation of blood pressure.

9. *Headache:* Onset or exacerbation of migraine or development of headache of a new pattern which is recurrent, persistent, or severe, requires discontinuation of oral contraceptiv

10. *Bleeding Irregularities:* Breakthrough bleeding, spotting, and amenorrhea are frequent reasons for patients discontinuing oral contraceptives. In breakthrough bleeding, nonfunctio causes should be borne in mind. In undiagnosed abnormal bleeding from the vagina, adequa diagnostic measures are indicated to rule out pregnancy or malignancy.

Women with a past history of oligomenorrhea or secondary amenorrhea, or young women without regular cycles should be advised that they may have a tendency to remain anovulatc or to become amenorrheic after discontinuation of oral contraceptives.

11. *Ectopic Pregnancy:* Ectopic as well as intrauterine pregnancy may occur in contracept failures.

12. *Breast Feeding:* Oral contraceptives may interfere with lactation. Furthermore, a small fraction of the hormonal agents in oral contraceptives has been identified in the milk of moth receiving these drugs.

PRECAUTIONS
1. A complete medical and family history should be taken prior to the initiation of oral contraceptives. The pretreatment and periodic physical examinations should include specia reference to blood pressure, breasts, abdomen, and pelvic organs, including Papanicolaou smear and relevant laboratory tests. As a general rule, oral contraceptives should not be prescribed for longer than one year without another examination.
2. Preexisting uterine leiomyomata may increase in size.
3. Patients with a history of psychic depression should be carefully observed and the drug discontinued if depression recurs to a serious degree.
4. Oral contraceptives may cause fluid retention and should be prescribed with caution, ar only with careful monitoring, in patients with conditions which might be aggravated.
5. Patients with a past history of jaundice during pregnancy have an increased risk of recurrence of jaundice. If jaundice develops, the medication should be discontinued.
6. Steroid hormones may be poorly metabolized and should be administered with caution i patients with impaired liver function.
7. Users may have disturbances in normal tryptophan metabolism, which may result in a relative pyridoxine deficiency.
8. Serum folate levels may be depressed.
9. The pathologist should be advised of oral contraceptive therapy when relevant specime are submitted.
10. Certain endocrine and liver function tests and blood components may be affected. (a) Increased sulfobromophthalein retention. (b) Increased prothrombin and factors VII, VI IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregabili (c) Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone. (d) Decreased pregnanediol excretion. (e) Reduced response to metyrapone test.

Drug interactions: Reduced efficacy and increased incidence of breakthrough bleeding ha been associated with concomitant use of rifampin and an association has been suggested w barbiturates, phenylbutazone, phenytoin sodium, and ampicillin.

ADVERSE REACTIONS
An increased risk of the following serious adverse reactions has been associated with oral contraceptives.

Thrombophlebitis; Pulmonary embolism; Coronary thrombosis; Cerebral thrombosis; Cerebral hemorrhage; Hypertension; Gallbladder disease; Benign hepatomas; Congenital anomalies.

There is evidence of an association between the following conditions and the use of oral contraceptives, although additional confirmatory studies are needed. Mesenteric thrombosi Neuro-ocular lesions, eg, retinal thrombosis and optic neuritis.

The following adverse reactions have been reported in patients receiving oral contraceptiv and are believed to be drug-related: Nausea and/or vomiting, usually the most common adverse reactions, occur in approximately 10 percent or less of patients during the first cycle Other reactions, as a general rule, are seen much less frequently or only occasionally: gastro testinal symptoms; breakthrough bleeding; spotting; change in menstrual flow; dysmenorrhea; amenorrhea during and after treatment; temporary infertility after discontinuance of treatment; edema; chloasma or melasma; breast changes; change in weight; change in cervical erosion and cervical secretion; possible diminution in lactation when given immediately post partum; cholestatic jaundice; migraine; increase in size of uterine leiomyomata; r (allergic); mental depression; reduced tolerance to carbohydrates; vaginal candidiasis; change in corneal curvature; intolerance to contact lenses.

The following adverse reactions have been reported and the association has been neither confirmed nor refuted.

Premenstrual-like syndrome; cataracts; changes in libido; chorea; changes in appetite; cystitis-like syndrome; headache; nervousness; dizziness; hirsutism; loss of scalp hair; erythema multiforme; erythema nodosum; hemorrhagic eruption; vaginitis; porphyria.

Special Notes on Administration
Loestrin 21 1.5/30 (1.5 mg norethindrone acetate and 30 mcg ethinyl estradiol tablets, USP)—Menstruation usually begins two or three days, but may begin as late as the fourth or fifth day, after discontinuing medication.

Loestrin Fe 1.5/30—Menstruation usually begins two or three days, but may begin as late the fourth or fifth day, after the brown ferrous fumarate tablets have been started.

Because of the relatively low estrogenic content, Loestrin 1.5/30 is not a good cyclic regula tor. There are patients whose inherent hormone balance will require larger amounts of estrog than that contained in Loestrin 1.5/30 to achieve cyclic regularity. These patients experience altered bleeding patterns, which do not conform to treatment schedules.

The physician should be alert to the fact that the irregular bleeding patterns could mask bleeding from organic cause, and appropriate diagnostic measures should be taken if the bleeding persists or continues after changing to a higher estrogen-content product.

After several months, bleeding may be reduced to a virtual absence; reduced flow may be a result of medication and not indicative of pregnancy.

HOW SUPPLIED
Loestrin Fe 1.5/30 is available in compacts each containing 21 green tablets and 7 brown tablets. Each green tablet contains 1.5 mg of norethindrone acetate and 30 mcg of ethinyl estradiol. Each brown tablet contains 75 mg of ferrous fumarate. Available in packages of five compacts and packages of five refills.

Loestrin 21 1.5/30 is available in compacts each containing 21 tablets. Each green tablet contains 1.5 mg of norethindrone acetate and 30 mcg of ethinyl estradiol. Available in packages of five compacts and packages of five refills.

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[1] First Health and Nutrition Survey, HEW Pub. No. (HRA) 74-1219-1.
[2] Herbert, V.—Current Concepts in Nutrition 5. 79 (1977)

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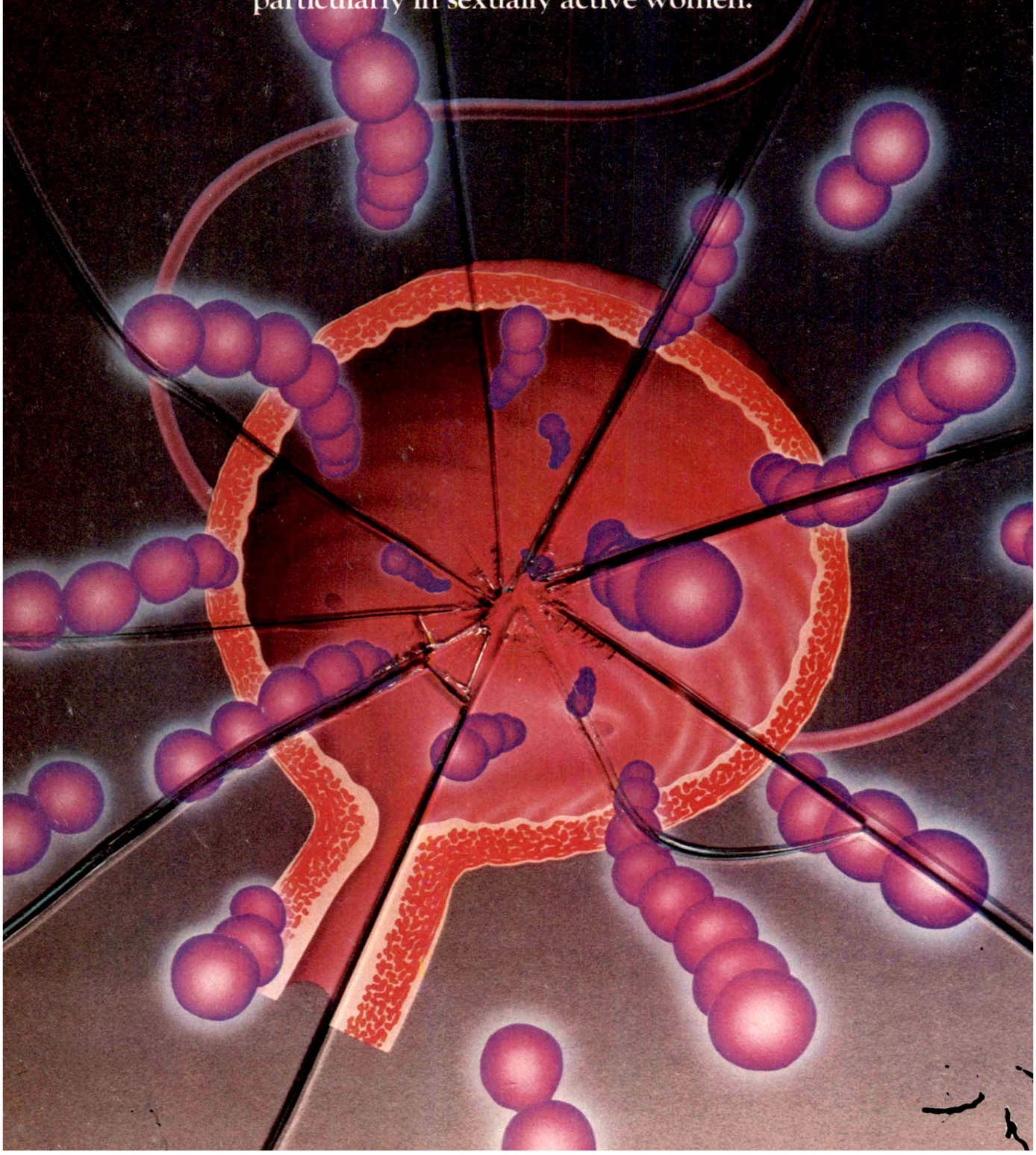
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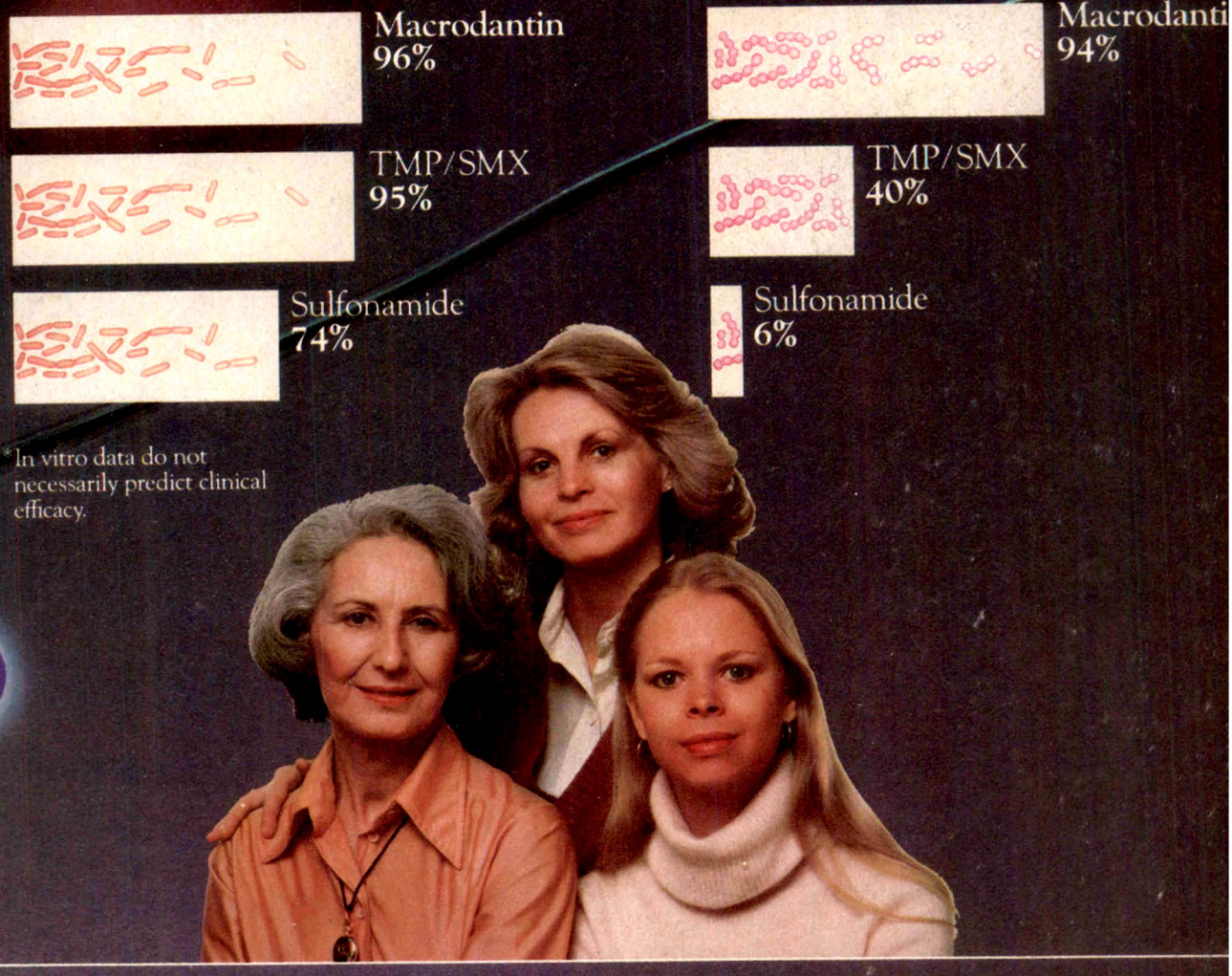
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INDICATIONS: Macrodantin is indicated for the treatment of urinary tract infections when due to susceptible strains of *Escherichia coli*, enterococci, *Staphylococcus aureus* (it is not indicated for the treatment of associated renal cortical or perinephric abscesses), and certain susceptible strains of *Klebsiella* species, *Enterobacter* species, and *Proteus* species.
NOTE: Specimens for culture and susceptibility testing should be obtained prior to and during drug administration.
CONTRAINDICATIONS: Anuria, oliguria, or significant impairment of renal function (creatinine clearance under 40 ml per minute) are contraindications to therapy with this drug. Treatment of this type of patient carries an increased risk of toxicity because of impaired excretion of the drug. For the same reason, this drug is much less effective under these circumstances.

The drug is contraindicated in pregnant patients at term as well as in infants under one month of age because of the possibility of hemolytic anemia due to immature enzyme systems (glutathione instability).

The drug is also contraindicated in those patients with known hypersensitivity to Macrodantin, Furadantin® (nitrofurantoin), and other nitrofurantoin preparations.
WARNINGS: Acute, subacute and chronic pulmonary reactions have been observed in patients treated with nitrofurantoin products. If these reactions occur, the drug should be withdrawn and appropriate measures should be taken.

An insidious onset of pulmonary reactions (diffuse interstitial pneumonitis or pulmonary fibrosis, or both) in patients on long-term therapy warrants close monitoring of these patients.

There have been isolated reports giving pulmonary reactions as a contributing cause of death. (See Hypersensitivity reactions.)

Cases of hemolytic anemia of the primaquine sensitivity type have been induced by Macrodantin. The hemolysis appears to be linked to a glucose-6-phosphate dehydrogenase deficiency in the red blood cells of the affected patients. This deficiency is found in 10 percent of Negroes and a small percentage of ethnic groups of Mediterranean and Near-Eastern origin. Any sign of hemolysis is an indication to discontinue the drug. Hemolysis ceases when the drug is withdrawn.

Pseudomonas is the organism most commonly implicated in superinfections in patients treated with Macrodantin.
PRECAUTIONS: Peripheral neuropathy may occur with Macrodantin therapy; this may become severe or irreversible. Fatalities have been reported. Predisposing conditions such as renal impairment (creatinine clearance under 40 ml per minute), anemia, diabetes, electrolyte imbalance, vitamin B deficiency, and debilitating disease may enhance such occurrence.
Usage in Pregnancy: The safety of Macrodantin during pregnancy and lactation has not been established. Use of this drug in women of childbearing potential requires that the anticipated benefit be weighed against the possible risks.
ADVERSE REACTIONS: Gastrointestinal reactions: Anorexia, nausea and emesis are the most frequent reactions; abdominal pain and diarrhea occur less frequently. These dose-related toxicity reactions can be minimized by reduction of dosage, especially in the female patient. Hepatitis occurs rarely.
Hypersensitivity reactions: Pulmonary sensitivity reactions may occur, which can be acute, subacute, or chronic.

Acute reactions are commonly manifested by fever, chills, cough, chest pain, dyspnea, pulmonary infiltration with consolidation or pleural effusion on x-ray, and eosinophilia. The acute reactions usually occur within the first week of treatment and are reversible with cessation of therapy. Resolution may be dramatic.

In subacute reactions, fever and eosinophilia are observed less often. Recovery is somewhat slower, perhaps as long as several months. If the symptoms are not recognized as being drug related and nitrofurantoin is not withdrawn, symptoms may become more severe.

Chronic pulmonary reactions are more likely to occur in patients who have been on continuous nitrofurantoin therapy for six months or longer. The insidious onset of malaise, dyspnea on exertion, cough, and altered pulmonary function are common manifestations. Roentgenographic and histologic findings of diffuse interstitial pneumonitis or fibrosis, or both, are also common manifestations. Fever is rarely prominent.

The severity of these chronic pulmonary reactions and the degree of their resolution appear to be related to the duration of therapy after the first clinical signs appear. Pulmonary function may be permanently impaired even after cessation of nitrofurantoin therapy. This risk is greater when pulmonary reactions are not recognized early.
Dermatologic reactions: Maculopapular, erythematous, or eczematous eruption, pruritus, urticaria, and angioedema.
Other sensitivity reactions: Anaphylaxis, asthmatic attack in patients with history of asthma, cholestatic jaundice, drug fever, and arthralgia.
Hematologic reactions: Hemolytic anemia, granulocytopenia, leukopenia, eosinophilia, and megaloblastic anemia. Return of the blood picture to normal has followed cessation of therapy.
Neurological reactions: Peripheral neuropathy, headache, dizziness, nystagmus, and drowsiness.
Miscellaneous reactions: Transient alopecia. As with other antimicrobial agents, superinfections by resistant organisms may occur. With Macrodantin, however, these are limited to the genitourinary tract because suppression of normal bacterial flora elsewhere in the body does not occur.

References: 1. Center for Disease Control: *National Nosocomial Infections Study Report*, Annual Summary 1976, issued February 1978. Washington, DC, U.S. Department of Health, Education, and Welfare, p 8. 2. Cooper J, et al: Diagnostic and chemoprophylactic importance of perineal microbial carriage, in Siegenthaler W, Luthy R (eds): *Current Chemotherapy*. Washington, DC, American Society for Microbiology, 1978, vol 1, pp 198-200. 3. Buckley RM, McGuckin M, MacGregor RR: Urine bacterial counts after sexual intercourse. *N Engl J Med* 298:321-324, 1978. 4. PMR Bacteriologic Report, Summer Series, 1978; a national bacteriologic monitoring service for 200 acute-care hospitals of 100 beds or more.

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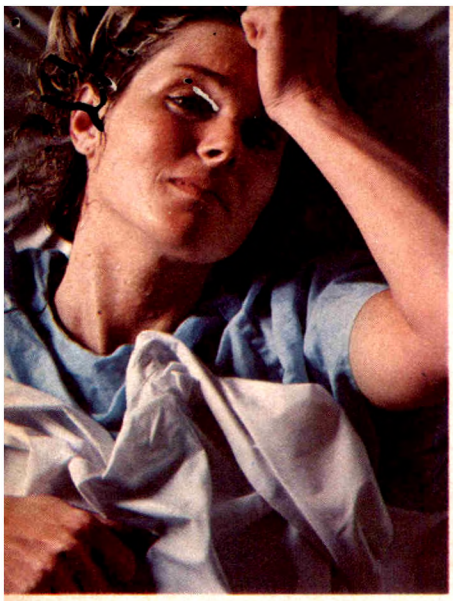
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BRIEF SUMMARY
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PREMARIN® Brand of Conjugated Estrogens Tablets, U.S.P.

1. ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA.

Three independent case control studies have reported an increased risk of endometrial cancer in postmenopausal women exposed to exogenous estrogens for more than one year.[1-3] This risk was independent of the other known risk factors for endometrial cancer. These studies are further supported by the finding that incidence rates of endometrial cancer have increased sharply since 1969 in eight different areas of the United States with population-based cancer reporting systems, an increase which may be related to the rapidly expanding use of estrogens during the last decade.[4] The three case control studies reported that the risk of endometrial cancer in estrogen users was about 4.5 to 13.9 times greater than in nonusers. The risk appears to depend on both duration of treatment[1] and on estrogen dose.[3] In view of these findings, when estrogens are used for the treatment of menopausal symptoms, the lowest dose that will control symptoms should be utilized and medication should be discontinued as soon as possible. When prolonged treatment is medically indicated, the patient should be reassessed on at least a semiannual basis to determine the need for continued therapy. Although the evidence must be considered preliminary, one study suggests that cyclic administration of low doses of estrogen may carry less risk than continuous administration;[3] it therefore appears prudent to utilize such a regimen. Close clinical surveillance of all women taking estrogens is important. In all cases of undiagnosed persistent or recurring abnormal vaginal bleeding, adequate diagnostic measures should be undertaken to rule out malignancy. There is no evidence at present that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic doses.

2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY.

The use of female sex hormones, both estrogens and progestogens, during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a non-steroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare.[5,6] This risk has been estimated as not greater than 4 per 1000 exposures.[7] Furthermore, a high percentage of such exposed women (from 30 to 90 percent) have been found to have vaginal adenosis,[8-12] epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether they are precursors of malignancy. Although similar data are not available with the use of other estrogens, it cannot be presumed they would not induce similar changes. Several reports suggest an association between intrauterine exposure to female sex hormones and congenital anomalies, including congenital heart defects and limb reduction defects.[13-16] One case control study[16] estimated a 4.7-fold increased risk of limb reduction defects in infants exposed in utero to sex hormones (oral contraceptives, hormone withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some of these exposures were very short and involved only a few days of treatment. The data suggest that the risk of limb reduction defects in exposed fetuses is somewhat less than 1 per 1000. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well controlled studies that progestogens are effective for these uses. If PREMARIN is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the advisability of pregnancy continuation.

DESCRIPTION: PREMARIN (Conjugated Estrogens Tablets, U.S.P.) for oral administration contains a mixture of estrogens, obtained exclusively from natural sources, blended to represent the average composition of material derived from pregnant mares' urine. It contains estrone, equilin, and 17α-dihydroequilin, together with smaller amounts of 17α-estradiol, equilenin, and 17α-dihydroequilenin as salts of their sulfate esters.

INDICATIONS: Based on a review of PREMARIN Tablets by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications for use as follows:

Effective:

1. Moderate to severe *vasomotor* symptoms associated with the menopause. (There is no evidence that estrogens are effective for nervous symptoms or depression without associated vasomotor symptoms, and they should not be used to treat such conditions.)
2. Atrophic vaginitis.
3. Kraurosis vulvae.
4. Female hypogonadism.
5. Female castration.
6. Primary ovarian failure.
7. Breast cancer (for palliation only) in appropriately selected women and men with metastatic disease.
8. Prostatic carcinoma—palliative therapy of advanced disease.
9. Postpartum breast engorgement—Although estrogens have been widely used for the prevention of postpartum breast engorgement, controlled studies have demonstrated that the incidence of significant painful engorgement in patients not receiving such hormonal therapy is low and usually responsive to appropriate analgesic or other supportive therapy. Consequently, the benefit to be derived from estrogen therapy for this indication must be carefully weighed against the potential increased risk of puerperal thromboembolism associated with the use of large doses of estrogens.[19]

PREMARIN HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING).

"Probably" effective: For estrogen deficiency-induced osteoporosis, and only when used in conjunction with other important therapeutic measures such as diet, calcium, physiotherapy, and good general health-promoting measures. Final classification of this indication requires further investigation.

CONTRAINDICATIONS: Estrogens should not be used in women (or men) with any of the following conditions: 1. Known or suspected cancer of the breast except in appropriately selected patients being treated for metastatic disease. 2. Known or suspected estrogen-dependent neoplasia. 3. Known or suspected pregnancy (See Boxed Warning). 4. Undiagnosed abnormal genital bleeding. 5. Active thrombophlebitis or thromboembolic disorders. 6. A past history of thrombophlebitis, thrombosis, or thromboembolic disorders associated with previous estrogen use (except when used in treatment of breast or prostatic malignancy).

WARNINGS: At the present time there is no satisfactory evidence that estrogens given to postmenopausal women increase the risk of cancer of the breast,[17] although a recent study has raised this possibility.[18] There is a need for caution in prescribing estrogens for women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms. A recent study has reported a 2- to 3-fold increase in the risk of surgically confirmed gallbladder disease in women receiving postmenopausal estrogens.[17]

Adverse effects of oral contraceptives may be expected at the larger doses of estrogen used to treat prostatic or breast cancer or postpartum breast engorgement; it has been shown that there is an increased risk of thrombosis in men receiving estrogens for prostatic cancer and women for postpartum breast engorgement.[19-22] Users of oral contraceptives have an increased risk of diseases, such as thrombophlebitis, pulmonary embolism, stroke, and myocardial infarction.[23-30] Cases of retinal thrombosis, mesenteric thrombosis, and optic neuritis have been reported in oral contraceptive users.[31,32] An increased risk of postsurgery thromboembolic complications has also been reported in users of oral contraceptives.[33,34] If feasible, estrogen should be discontinued at least 4 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization. Estrogens should not be used in persons with active thrombophlebitis, thromboembolic disorders, or in persons with a history of such disorders in association with estrogen use. They should be used with caution in patients with cerebral vascular or coronary artery disease. Large doses (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown[35] to increase the risk of nonfatal myccardial infarction, pulmonary embolism and thrombophlebitis. When doses of this size are used, any of the thromboembolic and thrombotic adverse effects should be considered a clear risk.

Benign hepatic adenomas should be considered in estrogen users having abdominal pain and tenderness, abdominal mass, or hypovolemic shock. Hepatocellular carcinoma has been reported in women taking estrogen-containing oral contraceptives.[36] Increased blood pressure may occur with use of estrogens in the menopause[37] and blood pressure should be monitored with estrogen use. A worsening of glucose tolerance has been observed in patients on estrogen-containing oral contraceptives. For this reason, diabetic patients should be carefully observed. Estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases.

PRECAUTIONS: Physical examination and a complete medical and family history should be taken prior to the initiation of any estrogen therapy with special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolau smear. As a general rule, estrogen should not be prescribed for longer than one year without another physical examination being performed. Conditions influenced by fluid retention such as asthma, epilepsy, migraine, and cardiac or renal dysfunction, require careful observation. Certain patients may develop manifestations of excessive estrogenic stimulation, such as abnormal or excessive uterine bleeding, mastodynia, etc. Oral contraceptives appear to be associated with an increased incidence of mental depression.[23a] Patients with a history of depression should be carefully observed. Preexisting uterine leiomyomata may increase in size during estrogen use. The pathologist should be advised of estrogen therapy when relevant specimens are submitted. If jaundice develops in any patient receiving estrogen, the medication should be discontinued while the cause is investigated. Estrogens should be used with care in patients with impaired liver function, renal insufficiency, metabolic bone diseases associated with hypercalcemia, or in young patients in whom bone growth is not complete.

The following changes may be expected with larger doses of estrogen:

a. Increased sulfobromophthalein retention.

b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.

c. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by PBI, T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered.

d. Impaired glucose tolerance.

e. Decreased pregnanediol excretion.

f. Reduced response to metyrapone test.

g. Reduced serum folate concentration.

h. Increased serum triglyceride and phospholipid concentration.

As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk.

ADVERSE REACTIONS: The following have been reported with estrogenic therapy, including oral contraceptives: breakthrough bleeding, spotting, change in menstrual flow; dysmenorrhea; premenstrual-like syndrome, amenorrhea during and after treatment; increase in size of uterine fibromyomata; vaginal candidiasis, change in cervical erosion and in degree of cervical secretion; cystitis-like syndrome; tenderness, enlargement, secretion (of breasts); nausea, vomiting, abdominal cramps, bloating; cholestatic jaundice; chloasma or melasma which may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair, hirsutism; steepening of corneal curvature; intolerance to contact lenses; headache, migraine, dizziness, mental depression, chorea; increase or decrease in weight; reduced carbohydrate tolerance; aggravation of porphyria; edema; changes in libido.

ACUTE OVERDOSAGE: May cause nausea, and withdrawal bleeding may occur in females.

DOSAGE AND ADMINISTRATION: 1. *Given cyclically for short term use only:* For treatment of moderate to severe *vasomotor* symptoms, atrophic vaginitis, or kraurosis vulvae associated with the menopause (0.3 to 1.25 mg or more daily).

The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible.

Administration should be cyclic (*e.g.*, three weeks on and one week off).

Attempts to discontinue or taper medication should be made at three to six month intervals.

2. *Given cyclically:* Female hypogonadism. Female castration. Primary ovarian failure. Osteoporosis.

Female hypogonadism—2.5 to 7.5 mg daily, in divided doses for 20 days, followed by a rest period of 10 days' duration. If bleeding does not occur by the end of this period, the same dosage schedule is repeated. The number of courses of estrogen therapy necessary to produce bleeding may vary depending on the responsiveness of the endometrium.

If bleeding occurs before the end of the 10 day period, begin a 20 day estrogen-progestin cyclic regimen with PREMARIN (Conjugated Estrogens Tablets, U.S.P.), 2.5 to 7.5 mg daily in divided doses, for 20 days. During the last five days of estrogen therapy, give an oral progestin. If bleeding occurs before this regimen is concluded, therapy is discontinued and may be resumed on the fifth day of bleeding.

Female castration and primary ovarian failure—1.25 mg daily, cyclically. Adjust upward or downward according to response of the patient. For maintenance, adjust dosage to lowest level that will provide effective control.

Osteoporosis (to retard progression)—1.25 mg daily, cyclically.

3. *Given for a few days:* Prevention of postpartum breast engorgement—3.75 mg every four hours for five doses, or 1.25 mg every four hours for five days.

4. *Given chronically:* Inoperable progressing prostatic cancer—1.25 to 2.5 mg three times daily.

Inoperable progressing breast cancer in appropriately selected men and postmenopausal women—10 mg three times daily for a period of at least three months.

Patients with an intact uterus should be monitored for signs of endometrial cancer and appropriate measures taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

HOW SUPPLIED: PREMARIN (Conjugated Estrogens Tablets, U.S.P.) No. 865—Each *purple* tablet contains 2.5 mg in bottles of 100 and 1,000. No. 866—Each *yellow* tablet contains 1.25 mg in bottles of 100 and 1,000. Also in unit dose package of 100. No. 867—Each *red* tablet contains 0.625 mg in bottles of 100 and 1,000. Also in unit dose package of 100. No. 868—Each *green* tablet contains 0.3 mg in bottles of 100 and 1,000.

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1. Fleury, F.J.: Obstet. Gynecol. News 12:1,25, Aug. 15, 1977.
2. Gardner, H.L., and Kaufman, R.H.: Benign Diseases of the Vulva and Vagina, St. Louis, The C.V. Mosby Company, 1969, p. 191.

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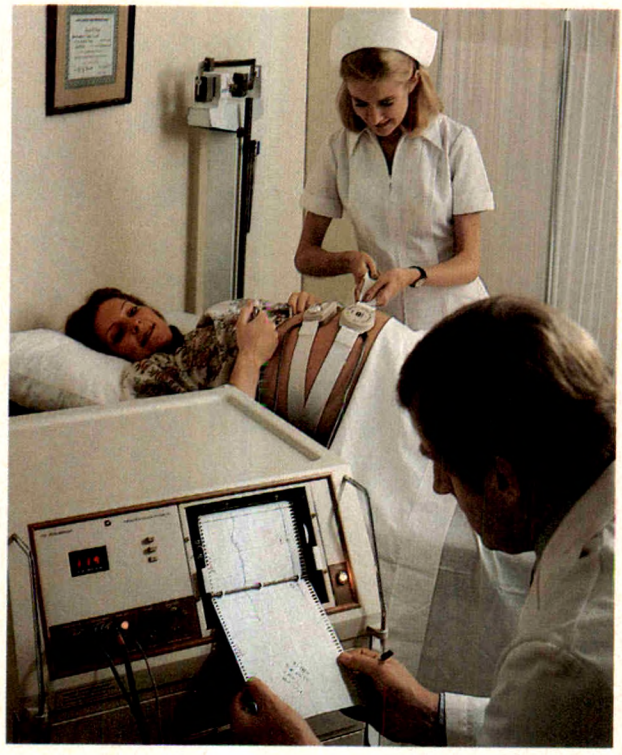
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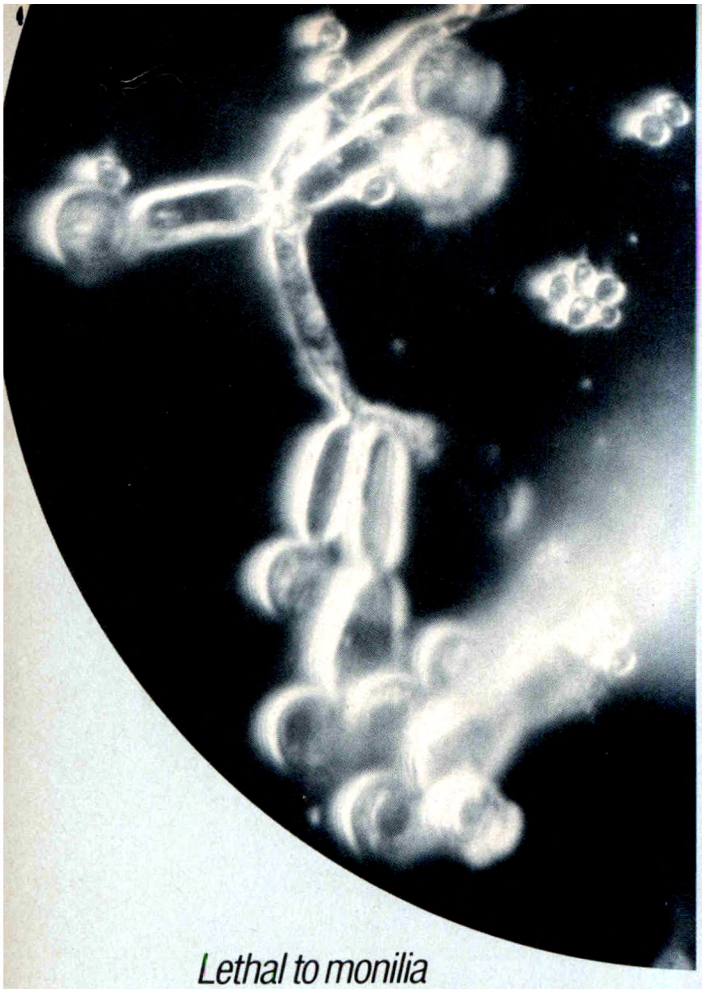
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1. Caraway, A.F.: Florida's Experience with an Intrauterine Device for the Nulliparous Patient. Presented at the International Family Planning Research Association Meeting, Palm Springs, California, October 21, 1974.
2. Caraway, A.F. and Vaughn, B.J.: J. Reprod. Med. *10*:170, April 1973.

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Medical Removal	15.6 (4.8-18.7)	23.2 (9.0-27.0)
Continuation Rate	70.4 (55.2-88.0)	59.8 (57.0-81.5)

3. Hayes, O.J.: A Clinical Evaluation of the Intrauterine Device for Control of Conception. South. Med. J. *66*:254, Feb. 1973.
4. Laufe, L.E., *et al.*: An Evaluation of the Use-effectiveness of the Saf-T-Coil in Private Practice. Contraception 9:23 1974.
5. Solish, G.I. and Majzlin, G.: The Majzlin Spring IUCD. Presented at the Sixth Annual Meeting of the Am. Assoc. of Planned Parenthood Physicians, Apr. 16-17, 1968.
6. Tietze, C. and Lewitt, S.: Evaluation of Intrauterine Devices: Ninth Progress Report of the Cooperative Statistical Program Studies in Family Planning. A Publication of the Population Council, No. 55, 1970.
7. Tietze, C.: Report of a New IUD: The Double Coil. Advances in Planned Parenthood, III:85, 1967.

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American Journal of Obstetrics and Gynecology

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EDITORIAL

Transfusion therapy in pregnant sickle cell disease patients

A CONSENSUS DEVELOPMENT CONFERENCE on Transfusion Therapy in Pregnant Sickle Cell Disease Patients was held at the National Institutes of Health on April 23-24, 1979.

In general, four consensus work groups explored the question of whether there was sufficient evidence about transfusion therapy to advocate its use to treat pregnant patients with sickle cell disease. Other aspects of treatment of sickle cell disease addressed included the need for further research, including clinical research, perinatal considerations, and sociomedical issues. The work groups were divided into four subject areas—the need for further research, clinical research approaches, perinatal considerations, and sociomedical issues. Each group then reached conclusions on its subject.

Work Group I

Further research in transfusion therapy for pregnant patients with sickle cell disease is needed, but the question must be approached in a systematic fashion.

In transfusion therapy, patients are divided into two major groups for management. Group 1 is treated symptomatically, but the majority of these patients still receive blood components. Blood transfusions are used whenever judged to be necessary but are not given prophylactically. Group 2 is treated with prophylactic blood transfusions. Transfusion in this group is used to elevate the hemoglobin (Hgb) and hematocrit (Hct) significantly and to suppress Hgb S–containing cells, while replacing them with Hgb A cells. Other patients in Group 2 are managed with exchange transfusions.

The following question was posed: Have the positive effects of transfusion therapy been satisfactorily proved? The consensus of the group is that the value of transfusion therapy has not been proved. Although most studies regarding transfusion therapy have examined effects on maternal infection, toxemia, jaundice, anemia, sickle cell crisis, and hospitalization and on fetal growth retardation, perinatal mortality, and premature delivery, there is no consensus as to the effects of transfusion on these parameters. Some of the reasons for neither proving nor refuting the value of transfusion therapy are that the problems associated with sickle cell disease and pregnancy are not well defined, previously reported data are retrospective, there are no controls for gathering information about pregnancies in sickle cell disease patients, data regarding patients are not comparable among institutions, and pathophysiologic mechanisms leading to poor outcome in sickle cell disease patients are not understood.

The problems of the pregnant sickle cell disease patient must be defined before there can be an attempt to solve them. Which parameters to study and modify must be determined before the best outcome for both mother and infant can be sought. Because some of the pregnant sickle cell patients seem to be at low risk, a method must be found to determine which mothers need, and which do not need, transfusion therapy.

Studies of pregnant sickle cell patients may shed light on reasons for intrauterine growth retardation, reasons for and management of fetal stress and distress, and the importance of various parameters in determining

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the degree of risk for individual pregnant sickle cell patients.

Since the positive effects of transfusion therapy have been neither proved nor refuted, a task force for study design should be formed. The task force would develop a protocol for a prospective randomized study to determine the benefits and risks of transfusions in the pregnant sickle cell disease patient. To provide for an adequate data base, The National Cooperative Study of the Clinical Course of Sickle Cell Disease should be expanded to include additional perinatal information decided upon by a task force. Further input should come from interested perinatal centers. This "natural history" study has been funded by the National Institutes of Health for 5 years and involves 15 medical centers and 23 hospitals.

Studying the problem further indicates that the management of the pregnant sickle cell disease patient is not well established. The impact on the lay population and decisions of the sickle cell disease patient regarding future pregnancies should be carefully considered.

Work Group II

Further research is necessary to define the relationship between outcome and transfusion therapy during pregnancy. To be definitive, this research must be prospective and randomized. Since it is apparent that no one hospital or city has a sufficient patient population to perform such a study within a reasonable interval, a national cooperative multicenter approach should be utilized. The study should be integrated with the ongoing "natural history" study. To be well conducted, such an expensive and extensive task must be given priority, organized through mechanisms of the National Heart, Lung, and Blood Institute, and adequately funded.

Patients should not be excluded from the study on the basis of genotype, but criteria must be developed for those who will be included. For example, is the patient's history helpful? Should sickle B+ thalassemia and patients with $\geq 10\%$ hemoglobin F be included in the study?

Data must be accumulated to determine more fully the risks of transfusion, and methods must be defined for reducing transfusion risks to the minimum. Follow-up data are mandatory and must include careful collaboration among obstetricians, hematologists, pediatricians, pathologists, and blood banking personnel. In addition, blood-typing and blood-processing requirements must be carefully defined.

Patients should be randomized to transfusion or no-transfusion therapy in a prospective way after informed consent has been given. However, patients randomized to "no-transfusion" therapy may be transfused for specifically defined indications.

Data collection must start as early as possible, and the benefit and timing must be determined by the study design analysis group. Following initial therapy, frequent monitoring of high hemoglobin S levels must be performed and an upper limit defined (possibly from data from the natural history study) which, when exceeded, warrants repeat transfusion. Additionally, maximum hemoglobin levels not to be exceeded must be defined.

Work Group III

Perinatal considerations for transfusion therapy in sickle cell patients should address these questions: (1) How should patient monitoring be considered? (2) What are the challenges of intrapartum management? (3) What is the approach to infant follow-up?

A detailed series of clinical and laboratory procedures could be used to evaluate patients during the antepartum, intrapartum, and postpartum periods and to establish a data base. The comprehensive nature of the outline recommended reflects the importance of gathering complete data during pregnancy. Important retrospective information might be obtained from these data and prospective therapeutic guidelines developed.

Regardless of the specific guidelines followed for pregnant sickle cell patients, medical care should be provided in a tertiary center, with a joint effort among obstetricians, hematologists, and pediatricians. It should involve awareness of the clinical course of the disease process during pregnancy as well as therapeutic modalities that may modify the course and outcome of pregnancy. Infants born to sickle cell disease patients, who may or may not have had transfusion therapy during pregnancy, should be observed for a minimum of 2 years.

Since an appropriate study has not been performed to document its value, the detailed list of procedures prepared by the group should not be considered as recommendations for patient management.

Work Group IV

The data are insufficient to advocate a large-scale, nationwide policy of transfusion therapy or to reach definitive conclusions about ethical considerations. However, a study to determine (within 1 to 2 years) in a limited number of centers the value of therapeutic versus prophylactic transfusion in management should be undertaken. Justification would appear to be the marked difference in opinion as regards the value of various treatment modalities.

Any study design must consider psychological considerations, including patient and physician levels of awareness and knowledge, and must allow for prejudice or feelings concerning fear of transfusion, possible intimidation from the community regarding transfusion needle marks (confused with addiction), pressure on family for repeated blood donations, convenience factors favoring time of transfusion for physician versus patient, overprotectiveness of patient's family, and possible "addiction" of patient to transfusion. Economic, geographic, and educational data relating to patient and physician must be considered, and continual updating of information about the progress of the study for all concerned must be planned. Counseling should be available both before and after conception. Information about the value of amniocentesis in selected instances should be made available to patients. Any study design should take all of the psychosocial aspects into account.

Access to the study must be available to all patients who wish to become involved, but patients should not be coerced.

Informed consent should be obtained from all participants. Innovative methods, such as audiovisual presentations with subsequent question-and-answer sessions, should be developed to avoid coercion of patients. Patient feedback mechanisms to test levels of comprehension need to be developed. Paramedical personnel may need to be included.

Funding for patient care in such a study should be through private or public means and not by grant support. Analysis of data and reporting can be related to National Institutes of Health support, but patient-care funding cannot.

The presence of hemoglobin SS, SC, or sickle thalassemia, which constitute sickle cell disease, should not be the sole justification for either abortion or sterilization. These procedures should be performed on the basis of medical indications and/or patient desire. The medical and legal communities need to be apprised of this consensus.

The conference was supported by the National Heart, Lung, and Blood Institute, National Institutes of Health. At the National Institutes of Health, consensus development conferences bring together biomedical research scientists, practicing physicians, consumers, and others, as appropriate, in an effort to reach general agreement on the efficacy and safety of a medical technology.

Cochairmen for the consensus meeting were John C. Morrison, M.D., University of Tennessee, Memphis; and Henry Foster, M.D., Meharry Medical College, Nashville.

Transactions of the Forty-first Annual Meeting of the South Atlantic Association of Obstetricians and Gynecologists

The points of Osler's compass

Presidential address

CARROLL H. LIPPARD, M.D.
Lynchburg, Virginia

WHILE THERE HAVE BEEN notable advances and accomplishments during our professional lifetime, many of us are uneasy about the direction medicine has taken. The forces that control our professional lives seem to have passed out of our control.

At the heart of the problem is a deterioration in the rapport of the physician-patient relationship which was so salutary for all concerned in the past, but which is now threatened by increasing intrusion of the federal government, by a growing technological influence on the practice of medicine, and by an increasing emphasis on the business aspects of our practices. In such an atmosphere there is the risk that our sense of mission and satisfaction in our work may fade and that our respect for ourselves as physicians in the time-honored sense may be weakened. In the midst of plenty, anxiety stalks among us with velvet step.

It has long been permissible and customary for presidential remarks to follow a philosophical bent, often fortified by quotes from notable historic figures or the classic philosophers. But I want to call upon the wisdom of that famous contemporary American philosopher Satchel Paige. You may remember one of Satchel's famous aphorisms: "Don't look back! Somethin' may be gaining on you."

At a time when we wonder if we may have taken a wrong turn somewhere and may have lost our bearings, perhaps we should ignore Satchel's admonition and look back to an earlier age of medicine for a new compass course, adjusting our sextant to focus on the values and precepts of William Osler as he trod the halls of the University of Pennsylvania almost a century ago.

The attraction of the University of Pennsylvania School of Medicine for Southerners has been remarkable and of long duration. Prior to the Civil War there were 5,501 graduates of that institution.[1] More than three fourths were from the South. Twenty-five percent of the entire corps of Confederate Army surgeons were graduates of that single institution contrasted with only six percent of Union Army surgeons.[2]

Such traditions do not fade easily in the South. In our own generation many a young product of the postdepression, small-town South moved northward in annual migratory waves after completing the first two medical school years in southern institutions, a significant number heading for the University of Pennsylvania School of Medicine.

Wards B and D at the University Hospital were Osler's wards. The first medical students in the United States to go to the patient's bedside with their teacher for ward rounds did so with him on those wards.

Osler would never have left Canada to come to Philadelphia had not the University of Pennsylvania been going through one of its periodic power struggles. After the Chair of Clinical Medicine was vacated in 1884, the Board of Trustees was deadlocked between two candidates from within the institution. Compromising, they went outside and chose Osler.[3]

Presented at the Forty-first Annual Meeting of the South Atlantic Association of Obstetricians and Gynecologists, Hot Springs, Virginia, January 28-31, 1979.

Reprint requests: Dr. Carroll H. Lippard, 1910 Thomson Dr., Lynchburg, Virginia 24501.

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He really was not too impressive at first. His teaching colleague, William Pepper, was an outstanding lecturer, silver-tongued, facile with words. Not so with Osler. The lecture platform was not his favorite forum. He was halting in his speech, usually sitting on the edge of a table, swinging his feet and twisting his ear. When standing, he shifted his weight from one leg to the other. His wife remarked, "I wish Willie would not rub the calf of his leg with his other foot to stir up his ideas."[4]

On the wards it was a different matter. Since Pepper rarely appeared except for lectures, Osler had the wards almost to himself, spending most of each morning with the medical students examining patients. An ever-growing number of students followed him about. It was in this setting that Osler developed a unique chemistry with his patients and with his students at the bedside. Any reservations the students had about Osler's performance in the lecture hall were soon dispelled as they worked side by side with him in the wards.

There was no microscope at the University Hospital when Osler arrived.[5] He brought his own and within a month had set up shop under the hospital amphitheater seats, where he introduced this revolutionary diagnostic tool to his students.

An eclectic scholar, Osler seemed to have time for whatever interested him or wherever he was needed. An accomplished pathologist, he made himself available for autopsies at the Blockley dead house, next door to the hospital, leading his omnipresent student disciples through the gate in the old wall like the Pied Piper. He taught them to respect the autopsy room as medicine's temple of truth, where fact was separated from conjecture.

In 1889, Johns Hopkins, a Baltimore merchant, died a bachelor, leaving $7 million to be divided equally between a new university and a new hospital, each to bear his name. The Johns Hopkins Hospital was about to be born. After five years at the University of Pennsylvania, Osler accepted the position of professor of medicine and physician in chief at The Johns Hopkins Hospital. He brought with him his Philadelphia friend, Howard A. Kelly, of Kelly stitch fame, as professor of obstetrics and gynecology. In Osler's sixteen years at Johns Hopkins, the "Hopkins Four"—Welch, Kelly, Halstead, and Osler—created an institution and teaching program that became the model for present-day medical education.

Osler's final move came in 1905, when he left Johns Hopkins to become Regius Professor of Medicine at Oxford University in England. There he spent the final fourteen years of his life, acclaimed worldwide as the outstanding clinician and teacher of his era.

Scope of influence

The scope of Osler's influence was enormous. At the time of his arrival on the medical scene in the United States, most medical schools were proprietary in nature, operated for profit, and medicine was taught primarily in the lecture hall. By general custom the hall was rented by the professor, the student paying his tuition directly to the instructor. For the most part, bedside instruction was neither expected nor provided.

At the University of Pennsylvania and Johns Hopkins, Osler revolutionized medical education by bringing the medical student to the patient's bedside on the wards, using the patient himself as the primary vehicle for teaching. Lectures and textbooks became secondary. As he put it, "To study the phenomena of disease without books is to sail an uncharted sea, while to study books without patients is not to go to sea at all."[6]

The importance Osler accorded the change he wrought in medical education is manifest in his comment, "I desire no other epitaph than the statement that I taught medical students in the wards."[7] The traditions of ward rounds, clinical clerkships, and house officer–residency programs were his creations and our legacy.

He introduced and popularized some of the medical technology new to his era. In addition to initiating the use of the microscope in the University of Pennsylvania Hospital, he introduced into the United States in 1884 the binaural stethoscope which is still in universal use.[8]

His writing ability became apparent early in his career. In addition to more than 1,200 medical articles in his lifetime, he wrote extensively on natural history, the history of medicine, and the history of English literature.[9] The bibliography of his published works spans 132 pages.[10] His influence became worldwide with publication of *The Principles and Practice of Medicine* in 1892, which rapidly became the premier texbook of medicine. Sixteen editions were published, the last in 1947, appearing not only in English but in French, German, Spanish, Portugese, and Chinese translations.

Osler's most lasting influence was the degree to which he humanized medicine. He taught by word and example that clinical excellence and skill in the technologies of medicine are important prerequisites for medical practice, but to be a physician in the true sense of the word, there must be a genuine interest in and commitment to the patient above and beyond the disease itself—a higher obligation to serve as the patient's advocate, counselor, and protector. The assertion of

such a humanitarian requirement was particularly impressive coming, as it did, from the man who was universally viewed as the consummate clinician, educator, and medical author of his era.

Relevance for today

Osler has been gone for sixty years, but our generation, as those before us, seems drawn to him as to no other historical figure. A computer search of the past five years revealed fifty-four articles in the English language medical literature that referred to him in their titles. His was a lovely flame, whose smoke still gets in our eyes. He reminds us of what we could be, of what the noblest traditions of our profession are.

His world was not easy, medical or otherwise. Yet he possessed a set of inner directed principles that provided safe transit for him and the generation who relied on his guidance through the rocky narrows of his day. Might the compass that proved so reliable in providing direction for Osler still work? Might it point out the way we should go to heal the breach that disturbs our relationship with our patients, to restore our sense of mission as physicians? Let us take a closer look at some of Osler's guiding principles, the key points of the compass by which he traveled through life.

The points of Osler's compass

True North for Osler was his conception of the ethical and philosophic precepts which should govern our lives as physicians.

The son of a minister, he grew up in an atmosphere that gave high priority to making one's life of service to others. He viewed medicine as a calling whose real reward lay in helping others. In 1906 he addressed a group of his favorite people, medical students: "Get your relationship clearly defined. You are in this profession as a calling, not a business. . . .Once get down to a purely business level, your influence is gone and the true light of your life is dimmed."[11] On another occasion: "More than any other, the practitioner of medicine may illustrate the . . . great lesson that we are here not to get all we can out of life for ourselves but to try to make the lives of others happier. . . . The practice of medicine is an art, not a trade; a calling, not a business; a calling in which your heart will be exercised equally with your head."[12]

At the South point of Osler's North-South axis was the patient himself.

For Osler, the management of the medical problem proceeded only in the context of working for the welfare of the patient as a total human being. As advocate and counselor for his patient, he was concerned not only with his patient's disease, but with his family, economic security, and any other factor of importance to his patient.

According to his Johns Hopkins associate, J. M. T. Finney, "There was developed in him . . . the capacity of making each individual patient feel that he was personally interested in his or her case, not by number, but as an individual. This was not merely assumed interest with him, either; it was genuine. . . . One of his special characteristics was optimism; not of the foolish sort which . . . says all is well when it surely is not, but which grasps every opportunity . . . to turn the . . . patient's thought from self and gloomy forebodings. . . . Hope was the bright star to which he was constantly pointing."[13] But if the patient was beyond cure and on desperate ground, Osler was there to comfort and to counsel.

He viewed this type of relationship as the "art of medicine." If absent, no matter how skilled and well documented the clinical handling of the patient, he viewed that physician as a technician, not a true physician in the best sense of the word.

The East point of Osler's compass refers to his lifelong interest in education.

In addition to the transformation he effected in medical school education, he was one of the earliest proponents of continuing education for physicians. He cautioned the graduating students at McGill University in 1905 that the body of knowledge they carried with them would be current for five years at most. He urged a systematic program to remain current or, ten years later, be "dead mentally, . . . fit to do a routine practice, . . . but without any deep convictions and probably more interested in stocks or horses than in diagnosis or therapeutics."[14]

He recognized the obstacles that success may throw into our paths. "The ever-increasing demands of practice leave less and less time for study, and a first class man may lose touch with his subject through no fault of his own, but through an entanglement from outside affairs which he deeply regrets but which he cannot control."[15]

Osler held firm opinions about qualifications for teachers. First, they should have a high level of clinical competence in their field. While stressing the "art of medicine," he did not view it in any sense as a substitute for thorough scientific competence. Second, they should teach by example traits of gentleness, forbearance, and courtesy in dealing with patients. Third, they should demonstrate a sense of obligation to put something back into the profession, to pass on to those who follow some of the benefits which the profession had provided them. Fourth, Osler felt it essential that teachers be involved in some degree with private prac-

tice, not for the sake of additional income, but to make them more aware of the actual conditions under which the student would be practicing in the future. Thus, he opposed the full-time teaching concept. "I cannot imagine anything more subversive to the highest ideal of a clinical school than to turn over young men who are to be our best practitioners to a group of teachers who are . . . out of touch with the conditions under which these young men will live."[16]

Osler's final compass point, West, was his way of life.

Osler related that while a junior in medical school in Montreal he was in a period of considerable anxiety. "Much worried as to the future, partly about final examinations, partly about what I should do afterwards, I picked up a volume of Carlyle, and on the page I opened there was the sentence, 'Our main business is not to see what lies dimly at a distance, but to do what lies clearly at hand'."[17] It seemd to Osler that life suddenly came into clear focus. He resolved to dismiss every anxiety from his mind and concentrate solely on putting his best into the next twenty-four hours. It was the starting point of a life attitude. He divided his life into "daytight" compartments, concentrating on doing justice to that twenty-four hour unit, not allowing himself to be distracted by concerns of past or future.

Osler speaks of the past: "Shut out the yesterdays—the petty annoyances, the real and fancied slights, the trivial mistakes, the disappointments, the sins, the sorrows, even the joys—bury them deep in the oblivion of each night. . . . Undress your soul at night . . . by shedding, as you do your garments, the daily sins, whether of omission or commission, and you will wake a free man with a new life."[18]

Osler bids us wall out the future as well. "The load of tomorrow, added to that of yesterday, carried today, makes the strongest falter. Shut off the future as tightly as the past. No dreams, no visions, no delicious fantasies, no castles in the air. . . . Nervous worries dog the steps of the man who is anxious about the future."[18] It was Osler's conviction that the only real influence we have on tomorrow hinges on how well we take care of today.

As for the day itself, he treated it as a precious thing, a slice of eternity given him by his Maker to be lived carefully and fully. "Join the whole creation of animate things in a deep heartfelt joy that you are alive, that you see the sun, that you are on this glorious earth which Nature has made so beautiful and which is yours to conquer and enjoy. . . . Realize that you have sixteen waking hours in which to accomplish the . . . objectives of that day. . . . Let each hour have its allotted duty, and cultivate that power of concentration which grows with its exercise so that the attention neither flags nor wavers, but settles with a bulldog tenacity on the subject before you. . . . No matter how trifling the matter at hand, do it with a feeling that it demands the best that is in you."[19]

He cautioned physicians against losing interest in everything but work and becoming one of the "bovine brethern who think of nothing but the treadmill and the corn."[20] His emphasis was on the balanced day and the balanced life.

He commented on the importance of a hobby, a happy marriage, and communion with the best minds of the ages through reading. "You will be a better man and not a worse practitioner for an avocation. I care not what it may be: gardening or farming, literature or history."[21] As for marriage, Osler wrote a former student who was contemplating matrimony, "You have a career ahead of you which the right woman will help, the wrong woman wreck. A level headed fellow can do anything he wishes with a wife if love blossom into trust, gentleness and consideration. A doctor needs a woman who will look after his house and rear his children, . . . whose first care will be for the home. Make her feel that she is your partner. . . . Consult her and take her advice about the house and children, but keep to yourself, as far as possible, the outside affairs relating to the practice."[22] Osler was happily married himself. At age 43 he married the great-granddaughter of Paul Revere, the widow of Dr. Samuel W. Gross, his longtime friend from Philadelphia days. Their only child, a son, they named Revere.

There was one further time allotment which Osler viewed as essential—a time reserved for reading the thoughts of the authors of the world's great literature. The final hour of his waking day, from ten to eleven o'clock, was spent in this fashion. It was from this hour that his broad sweep of interest in the humanities was continually recharged.

He urged us to meet the inevitable moments of stress and frustration with imperturbability and coolness under fire. He deliberately avoided strife from whatever quarter. "I have striven with none, not . . . because none was worth the strife, but because I have had a deep conviction of the hatefulness of strife, of its uselessness, of its disastrous effects, and a still deeper conviction of the blessings that come with . . . peace and concord."[23]

He was moved by the patience and forbearance with which the average man endured suffering. "Nothing will sustain you more . . . than the power to recognize in your humdrum routine . . . the true poetry of life—the poetry of the commonplace, of the ordinary man, of the plain toil-worn woman, with their loves and their joys, their sorrows and their griefs."[24]

Osler recognized that some of us will be called upon to face disappointment, failure, and even disaster. He expressed the hope that he himself might "cultivate such a measure of equanimity as . . . to be ready, when the day of sorrow and grief comes, to meet it with the courage befitting a man."[25] "You cannot hope . . . to escape from the cares and anxieties incident to . . . life. Stand up bravely, even against the worst. Your very hopes may have passed out of sight. . . . You may be left to struggle in the night alone. There is a struggle with defeat which some of you will have to bear. . . . Even with disaster ahead and ruin imminent, it is better to face them with a smile and with the head erect, than to crouch at their approach."[26]

Such a moment came to Osler himself. His only child, Revere, was killed in France in 1917. There was private heartbreak but no public grief. He wrote a friend, "Grief is a hard companion, particularly to an optimist and to one who has been a stranger to it for so many years. We decided to keep the flag flying, and let no outward action demonstrate . . . the aching hearts."[27]

In July, 1919, in his seventieth year, Osler developed a respiratory tract infection which was to be his terminal illness. It progressed to pneumonia and empyema. In the last days, before he became too ill to write, he sent brief notes to many of his close friends. His last note, six days before his death, contained the following sentence: "The harbour is not far off. And such a happy voyage! And such dear companions all the way. And the future does not worry."[28]

On December 29, 1919, this remarkable man passed from life into history, remaining true in the ordeal of his final illness and death to the qualities that made him an authentic hero to his generation. Our generation has not been fertile soil for heroes, medical or otherwise, but we could do worse than look to William Osler.

Comment

There are three areas that offer us the opportunity to claim some of Osler's ideals for our own.

First, we should adjust our personal compass to whatever degree may be necessary to ensure that our true North, as Osler's, is the welfare of each patient as a whole human being.

Our greatest professional fulfillment should come from our relationship with him as a total person rather than with his disease alone. We should endeavor to protect him from threats from any quarter, including from the marvels of our own specialty when this involves major financial expenditures in quest of technological data of interest but uncertain practical importance. We must recognize that the patient has a spectrum of aims and aspirations, of which his medical care is only one. Depletion of his economic resources by medical expense might severely impair his ability to achieve other of his life's objectives of exceeding importance to him. When this possibility exists, whatever our final recommendation to the patient, if it is made with full consideration given to all of his interests and responsibilities, Osler would be in accord with the decision as having been made on the right grounds.

Second, we, as private practitioners, should reclaim a central role in medical education.

Many medical teaching centers now find themselves under pressure from several directions. First, there has been widespread dispersion of the population away from university medical centers into suburbs and outlying communities. The population base from which clinical material was drawn for teaching purposes is no longer there. Second, university teaching centers are no longer the referral centers they once were. The residents whom they have trained so well over the past two decades are now located in those outlying communities, have excellent hospital facilities at their command, and encounter few medical problems which now require referral away from community hospitals into university centers. Third, medical schools are now faced with larger classes at the very time that the clinical material has dispersed. Fourth, capitation grants and other federal funds for medical education are falling increasingly into question, and funds to build additional beds at university centers are falling afoul of certificate-of-need requirements and constraints of federal and state budgets.

In the face of such changing conditions, patterns of medical education must change with them if our students and residents are to receive adequate clinical instruction. A fundamental prerequisite for any system of medical education has always been the availability of clinical material for teaching purposes. Willie Sutton, the bank robber of note, expressed the appropriate concept when asked why he robbed all those banks. His reply was, "Because that's where the money is." Medical education should occur where the patients are.

Those of us in private practice who have benefited so greatly from the teaching provided us by others in our training days should take note of our own developing opportunity to do the same for a new wave of medical students and residents in our community hospitals. At the same time, we must be aware of our responsibility to the student, the resident, and the medical school to ensure continuing quality of the teaching provided.

This process must be a two-way street. Departments of obstetrics and gynecology within our medical schools must reciprocally recognize their need to enter an educational partnership with community hospitals. There are obviously many problems and adjustments to be

worked out by all concerned, but our overriding priority should be to provide upcoming classes of students and residents exposure to a full range of clinical material under the best teachers and conditions possible, taking advantage of the strong points and assets of both university hospital and community hospital.

Third, we need to declare for ourselves an ethical tithe.

We live in an era when medicine is big business. Our offices hum with automated equipment. Our desks sag under stacks of third-party forms, reports, and regulations. We have had to devise a system dedicated to efficient delivery of medical care per unit of practice time.

This poses a dilemma. From its beginnings our profession has fostered a tradition of caring for those in genuine need without regard to time expended or financial reward, yet our system leans toward the impersonal and rewards efficiency.

To preserve the humanitarian side of medicine we must reserve a time to work outside the system, to disregard efficiency, and to treat ourselves to the pleasure of giving to some poor soul all the time he needs and the best of our skills in a thoroughly unbusinesslike way. To practice medicine with the expectation of compensation all along the way is to run the risk of extinguishing that fragile flame that lights our inner being and gives meaning to our lives. We must grasp the opportunity to exercise this ethical tithe, to give part of ourselves away, not so much for the patient and his welfare as for the nuturing of our own professional souls.

Conclusion

I have attempted to bring before you an outline of the life, attitudes, and values of William Osler. I do so with convictions born of twenty-five years of laboring with you in the medical vineyards that his beliefs and ideals remain realistic and practical and can restore a measure of peace and sense of mission to our lives. We will not always succeed, but in making the effort we will establish company with Osler in those ancient virtues he sought to exalt and preserve. The important thing for us is to claim those ideals for our own and attempt to incorporate them in a practical way into our individual lives. Osler realized that we would not always be successful in doing so. Even knowing this to be true, he tells us that we will be better men and truer physicians for the effort. In Osler's own words, "To have striven, to have made an effort, to have been true to certain ideals—this alone is worth the struggle."[29]

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Six years' experience with screening of a diethylstilbestrol-exposed population

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The physician population delivering obstetric care in Philadelphia between 1950 and 1970 was contacted to ascertain their use of diethylstilbestrol (DES) during pregnancy. Of the 31.8% of the physicians who responded to the questionnaire, 71.3% used DES during pregnancy and 12.7% desired assistance in review of their records. During the 6 years from the initial survey, 830 young women exposed to DES in utero were periodically screened for cervicovaginal abnormalities and clear cell adenocarcinoma. Of these 830 patients 67.7% were found to have cervicovaginal abnormalities, and 65.9% of the patients showed either adenosis or evidence of the prior existence of vaginal adenosis. Eight patients were treated for clear cell adenocarcinoma. Two cases were detected while asymptomatic. Seven of the patients are living with no evidence of cancer, and two of these have survived over 5 years. (AM. J. OBSTET. GYNECOL. 134:860, 1979.)

AFTER THE INITIAL REPORTS in 1972 by Herbst and associates[1, 2] describing the association of the maternal use during pregnancy of the synthetic steroid diethylstilbestrol (DES) with clear cell adenocarcinoma, adenosis, and other related vaginal abnormalities in female offspring, it became increasingly evident that many young women in the Philadelphia area were demonstrating these findings. In addition, because of the increased publicity devoted to this association by the lay press, a significant number of these women were seeking pelvic evaluation. In many of these patients a history of maternal DES therapy was confirmed by information from the patient's mother or from the mother's obstetrician. The Gynecologic Oncology Division of the Department of Obstetrics and Gynecology at the Hospital of the University of Pennsylvania felt it was important to locate and examine as many of the DES-exposed women as possible. A project was designed to locate the population at risk to DES exposure in utero in the greater Philadelphia area by contacting area physicians who might have used the drug in their practices and providing for them information and seminars aimed at locating the patients involved.

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Material and methods

Reaching the DES-exposed population. Dorland's Medical Directory between the years 1949 and 1970[3] was utilized to identify those physicians in the Philadelphia area who were cited as practicing obstetrics during those years. These physicians were then contacted by letter, which outlined the DES problem, provided information and a bibliography on exposure to DES in utero, and offered to them the services of trained personnel to try to locate the population at risk by review-

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ing their own practice files. In the initial letter, which was mailed to all these physicians, two questions were asked: (1) Did you use DES in your obstetric practice? (2) If you did use DES in your practice, would you avail yourself of the services that could be provided by the Hospital of the University of Pennsylvania? A list of gynecologists in the Philadelphia area familiar with DES-exposed women, as well as proficient in colposcopic examination of these patients, was provided.

Results

Between 1951 and 1970, a total of 718 obstetricians, gynecologists, and general practitioners delivered obstetric care in the Philadelphia area. Six hundred and seventy-eight (94.5%) of these physicians were located and 40 (5.5%) of these physicians could not be located. Of the 678 physicians in the Philadelphia area to whom the letters of information were mailed, 216 (31.8%) responded to the letter and 462 (68.2%) did not respond. Of those 216 physicians who responded to the questionnaire, 155 (71.8%) answered that they had used DES; 13 physicians (6%) were deceased and no information was available pertaining to their practices. One physician responded to the questionnaire but provided no information on his practice. Of the 47 physicians who used DES, 24 (59.1%) did not desire assistance, 15 (31.9%) informed us that they either had reviewed or were in the process of reviewing their own records, six (12.7%) desired assistance, and two (4.2%) declared that there were no records available for review.

The DES Evaluation Center. As of December, 1978, 830 young women had registered for examination and evaluation at the DES Center of the Hospital of the University of Pennsylvania. Six hundred and thirty-five were evaluated on two or more occasions. This paper will focus upon data from the initial visits of 830 patients. Twenty-six states were represented but the vast majority of the patients were born in the Delaware Valley area, representing Pennsylvania, New Jersey, and Delaware.

Although the initial referrals were generated primarily via the lay media (179 patients, 21.6%) family (70, 8.5%), or friends (50, 6.0%), the greatest number of referrals came from private physicians (470, 56.6%).

The age of the study population ranged from 7 to 35 years of age with 612 (73.5%) falling between the ages of 20 and 29. The population was 99.5% white (825 of 830).

Patient evaluation. At the time of the initial visit, a detailed medical history of the DES-exposed offspring was taken by a registered nurse. The data collected included a gynecologic history along with a record of any other pertinent medical information. The mother's gynecologic and obstetric history, especially with the pregnancy in question, as well as any drug dosage information was secured when possible. Since the three main sources for securing data are the delivering obstetrician's record, the pharmacy where the drug was purchased, and the hospital records where the patient was born, the patient was encouraged in the preliminary letter to exhaust all sources of information concerning the drug data.

The details of the examination were reviewed with the patient prior to entering the examination room. Depending on the age of the patient, more emphasis might have been placed on the details of her first gynecologic examination rather than the colposcopic examination.

Only rarely was it necessary to hospitalize the virginal DES-exposed patient for examination with anesthesia. Any patient presenting with complaints of irregular bleeding who could not be adequately evaluated in the outpatient center was admitted without delay for further evaluation with anesthesia. The actual gynecologic examination and colposcopic examination were performed as described by Townsend.[4]

Structural abnormalities. Gross structural cervicovaginal abnormalities were found in 512 (61.7%) of the individuals evaluated. One hundred eighty-seven (22.5%) patients were observed to have complete cervical collars; 96 (11.6%) were observed to have incomplete cervical collars; 185 (22.3%) were noted to have a "cock's comb" formation, and nine (1.1%) were observed to have transverse vaginal septa. Thirty-seven (4.5%) were lacking vaginal pars or fornices, and 45 patients (5.4%) had various other minor structural changes. Forty-seven (5.3%) had combinations of two or more structural changes in the cervix or vagina and forty-five (5.4%) had abnormalities that defied description.

Adenosis. Vaginal adenosis is the presence of glandular tissue similar to that found in other glandular müllerian elements. When the DES Study Center was initially opened, all patients had biopsies taken to prove the presence or absence of vaginal adenosis. As more and more individuals were examined, the necessity to take biopsies in order to prove the presence of vaginal adenosis was abandoned, and colposcopic identification of columnar epithelium in the vagina was considered adequate to document vaginal adenosis. In addition, a presumptive method of documenting vaginal adenosis, or the prior existence of vaginal adenosis, was the colposcopic identification of metaplastic squamous epithelium in the vagina. In 38 patients, vaginal adenosis existing alone was documented. In another 279 pa-

Table I. Results of Papanicolaou smears

Papanicolaou smear	*Patients*	
	No.	*%*
Class I	647	77.9
Class II	150	18.0
Class III	8	1.0
Class V	1	0.1
Not obtained	24	3.0
Total	830	100.0

Table II. Results of Papanicolaou smear interpretation

Results	*Patients*	
	No.	*%*
No abnormalities	572	68.9
Infection	31	3.7
Inflammation	56	6.7
Parakeratosis	29	3.5
Squamous metaplasia	61	7.3
Mild dysplasia	43	5.2
Moderate dysplasia	5	0.6
Severe	1	0.1
Carcinoma in situ	0	0.0
Other	32	3.9
Total	830	100.0

Table III. Frequency of abnormal colposcopic findings

Findings	*Patients*	
	No.	*%*
White epithelium	287	34.6
Punctations	195	23.5
Mosaic patterns	248	29.9
Atypical vessels	13	1.6
Keratosis	7	0.8

Table IV. Histologic results of colposcopically directed biopsies

Results	*Patients*	
	No.	*%*
No abnormalities	52	6.3
Inflammation	45	5.4
Parakeratosis	14	1.7
Squamous metaplasia	9	1.1
Mild dysplasia	22	2.7
Moderate dysplasia	4	0.5
Severe dysplasia	5	0.6
Adenocarcinoma	3	0.4
Other (tissue insufficient, etc.)	12	2.0
Vaginal adenosis	221	26.6
Total	375	47.3

tients metaplasia existing alone was noted in the vagina and in another 230 patients both metaplasia and adenosis coexisting in varying degrees were found. Thus 547 (65.9%) showed either adenosis or evidence of the prior existence of vaginal adenosis.

Abnormal Papanicolaou smears. Papanicolaou smears of the cervix, endocervix, and vaginal walls were obtained on all visits. One hundred fifty-nine (19.1%) patients had abnormal cytologic findings (Table I). Forty-nine of these patients had cytologic interpretations consistent with mild (43), moderate (five), and severe (one) dysplasia. There were no patients with cytology suggestive of carcinoma in situ (Table II).

Colposcopic findings. Colposcopic evaluation similarly showed disturbing results. The frequency of the abnormal colposcopic findings is noted in Table III. Over 35% of our patient population had one or more colposcopic abnormalities normally associated with dysplastic epithelium. The results of directed biopsies from colposcopically abnormal areas were much less disturbing. Colposcopically directed biopsies in 154 patients revealed dysplastic epithelium in only 31 patients. The majority of these patients (22) showed only mild dysplasia. When the results of the colposcopic findings were compared to the histologic results of biopsies taken from the areas of colposcopic abnormalities, it was obvious that the common colposcopic abnormalities used to identify abnormal epithelial changes, particularly white epithelium, punctation, and mosaic patterns, were unreliable in discerning areas of dysplastic epithelial changes in the DES-exposed population (Table IV).

Clear cell adenocarcinoma. Eight patients with clear cell adenocarcinoma of the vagina or cervix were seen. They ranged in age from 14 to 25, with a mean of 19.9. Each of the individuals was born during the decade of the 1950's (Table V).

Symptoms. Two of the patients were asymptomatic and were undergoing examination because of a known history of DES exposure in utero. Two of the patients had an abnormal vaginal discharge and four of the patients had irregular bleeding. Except for the two patients who were asymptomatic, the duration of symptoms in five of the other patients varied between 1 and 5 months, and in the last patient there was a history of postcoital bleeding for 2 years (Table VI). It should be noted that this latter patient had seen at least two gynecologists for examination, at which time "severe inflammation" of the cervix was noted, and because of normal cytologic findings nothing further was recommended. In seven of the eight patients, therefore, the

delay in diagnosis was felt to be insignificant. Seven of the eight patients had never had sexual intercourse.

Papanicolaou smears. Papanicolaou smears were not obtained in three of the patients since initial examination by the referring physician revealed an abnormality from which a direct biopsy was performed, which showed cancer. The patient who had the 2 year delay in diagnosis had negative cervical cytologic findings on several occasions. Of the remaining four patients, two had Class III cytologic smears, designated as "suspicious" or "rule out adenocarcinoma," while two of the patients had Class V vaginocervical cytologic findings consistent with adenocarcinoma.

Location and stage of carcinoma. Seven of the eight patients had carcinomas which were classified as clear cell adenocarcinoma of the cervix and one as clear cell adenocarcinoma of the vagina. Of the patients with cervical cancer one had a Stage IB lesion clinically, five had Stage IIA, and one patient had a Stage IIIB lesion. The last patient had celiotomy for surgical staging and was found at that time to have only an inflammatory process causing the parametrial induration. The patient with the vaginal carcinoma, Stage II, had a 1.5 cm polypoid lesion attached by a narrow stalk to the upper left lateral vagina, below the cervix, with minimal induration of the underlying vaginal tissues.

Treatment. Seven of the patients were treated by radical hysterectomy and bilateral para-aortic and pelvic lymphadenectomy. Two of the patients were found to have nodes involved with tumor and were given postoperative total pelvic radiation. The extent of the dissection of the vagina was based on the degree to which the vagina was involved with either the tumor or areas of adenosis. Total vaginectomy was never performed primarily and in no instance was grafting of the vaginal tract necessary. The technique of vaginal closure as described by Welch and colleagues[5] was carried out to increase the vaginal depth when radical hysterectomy was done. The one patient who was originally classified as having a Stage IIIB carcinoma of the cervix, prior to staging celiotomy, was treated by total pelvic radiation followed by total abdominal hysterectomy and bilateral salpingo-oophorectomy.

Survival. One of the patients who was treated by radical hysterectomy and pelvic lymphadenectomy developed fatal postoperative hepatic necrosis which was thought to be related to the use of halothane.* The other seven patients are all living and well, from 1 to 7 years, with a mean of 41.1 months. Two of the survivors have lived over 5 years. The longest survivor had two tumor-bearing nodes and received postoperative radiation.

One patient developed a limited focus of recurrence in the upper vagina 6 months following radical surgery, which was discovered on colposcopically directed biopsy. This was followed by resection of the upper half of the vagina and replacement of the area by a split-thickness skin graft. There has been no evidence of further recurrence in this patient 3 years after resection.

Associated DES changes. An evaluation of the associated DES changes found in these patients with clear cell adenocarcinoma of the cervix or vagina shows that all of the seven patients who were initially examined had evidence of adenosis on gross or colposcopic examination. In all seven, the gross lesions were also obvious. In addition, four had a partial or complete cervical collar, one had a "cock's comb," and one had a pseudopolyp of the cervix. The patient who had Stage IIIB disease could not be properly examined and therefore is not included in this evaluation.

In reviewing the DES background of the mothers of the patients with clear cell adenocarcinoma, there was a definite maternal DES history in six of the eight patients. In one there was a questionable history and in another no history of any type of medication could be ascertained. Only three of the eight mothers had a history of bleeding during pregnancy.

*Fluothane, Ayerst Labs.

Table V. Clear cell adenocarcinoma

Year of diagnosis	*Age of patient at diagnosis*	*Year of birth of patient*
1971	14	1957
1973	20	1953
1974	18	1956
1975	24	1951
1975	22	1953
1976	17	1959
1978	25	1953
1978	19	1959

Table VI. Clear cell adenocarcinoma—Duration of symptoms

Duration	*No. of patients*
No symptoms	2
1 mo.	2
2-5 mo.	3
2 yr.	1

Comment

The 30% response to the questionnaire sent to the physician population was disappointing. The nature of

the questions might have been interpreted by some to be threatening, since the maternal ingestion of DES and its subsequent association with adenocarcinoma of the vagina have resulted in a significant number of lawsuits. Although physicians are apparently not legally culpable for possible DES-induced sequelae a pointed inquiry as to the physicians' use of DES to preserve pregnancy may have discouraged a significant number of physicians from answering this question.

Another interesting finding was the fact that those physicians who used DES over half (51.1%) did not wish any assistance in reviewing their records. It is presumed that patient privacy was the primary reason for this response. It had been expected that such a tedious task as review of patient charts would have prompted a more positive response, especially since the review would have been performed by professional personnel. A review of the charts of those six physicians who used DES and desired our assistance in review of their charts located 563 young women exposed to DES in utero. An interesting question that will remain unanswered is whether our letter and questionnaire served to stimulate some physicians to review their own records. Since 31.9% of the physicians either had screened, were screening, or planned to screen their own records it can be presumed that this questionnaire was a positive force in this direction. Subsequent review of the records of 563 DES-exposed female subjects seen in our clinic has shown that 51.8% of the patients were sent to us by physicians.

The total number of structural abnormalities of the cervix and vagina (61.7%) was consistent with the findings of other investigators but our estimate of the presence of vaginal adenosis was greater than that first described by Sandberg[6] (43%) in a normal population and by Herbst and associates[2] in their initial report (33%) and similar to the findings of Burke and associates[7] (64% ± 5%).

These results, which are similar to those of other authors (Ng,[8] Burke and associates,[7] and Robboy and colleagues,[9] and Bibbo and co-workers[10]) show a much lower incidence of significant dysplastic squamous changes (1.1%) than that of earlier reports, which predicted a significant degree of squamous neoplasia (Fetherston[11] and Mattingly and Stafl[12]). The subjective element of these earlier, more alarming reports is evident. These data are also consistent with those of Burke and associates in emphasizing the lack of correlation between colposcopic abnormalities of the vaginal mucosa and the eventual histologic interpretation. White epithelium, punctation, and mosaic patterns are unreliable indicators of abnormal epithelial growth when found in the vaginal mucosa of the DES offspring.

The experience with clear cell adenocarcinoma and DES exposure in utero is consistent with the report by Herbst and Cole[13] of 333 young women with clear cell adenocarcinoma. An interesting finding is the higher incidence of carcinoma of the cervix in our patients, with only one being strictly vaginal. A total of 59.7% of the cases of clear cell adenocarcinoma reported to the Registry for Research on Hormonal Transplacental Carcinogenesis were confined to the vagina. The relatively short duration from the onset of symptoms to diagnosis is also striking since two of the patients had no symptoms and the cancer was discovered on routine examination because of DES exposure and since two had only increased nonbloody vaginal discharge. The value of screening of the DES-exposed population is reaffirmed.

Two of the patients were found to have pelvic lymph nodes involved with tumor, and postoperative radiation therapy was given to each patient. At present all seven of the patients who survived the operation are living and free of disease.

Each patient who had clear cell adenocarcinoma also had associated adenosis. The relation of these lesions suggests that the misplaced müllerian epithelium may have, because of its abnormal anatomic location, a tendency for malignant change. It does not, however, explain the development of clear cell adenocarcinoma in the cervix, where glandular epithelium is a normal component.

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Quality of life for the gynecologic oncology patient

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An attempt is made to define the quality of life in terms of the patient with gynecologic cancer. The effect of the diagnosis of cancer and its recurrence or its terminal state on the quality of life is considered. Possible methods of assessing the patient's individual feelings about the quality of her life are reviewed and suggestions made for incorporating these into plans of management at all stages of the disease. (AM. J. OBSTET. GYNECOL. 134:866, 1979.)

"QUALITY OF LIFE" is an intriguing and puzzling term. It is mentioned frequently in connection with gynecologic oncology patients, but if I asked for a definition of it I might get as many answers as there are people in the audience. This widespread use of the phrase without precise agreement on its meaning reminds me of what Dr. Dale Coman, Professor of Pathology at the University of Pennsylvania School of Medicine, told me many years ago. He said that if you want a subject for research you should take a generally accepted statement from a standard textbook and try to find out if it is true. Very often you will discover that it is only an opinion and is not supported by good data. The purpose of this paper, then, is to define what "quality of life" means, how it is affected by gynecologic cancer and its therapy, and how it may be included in the overall plans for patient care.

The life whose quality we are considering is composed of certain basic components (Table I). Body functions include the essentials of eating, excreting, activity, sexuality, and the presence or absence of pain. The worst thing that can happen to some people is to have one or another of these functions go wrong. For example, even the relatively minor nausea and vomiting which occasionally accompany the use of melphalan after operation in advanced cancer of the ovary may be almost intolerable to one woman. On the other hand, the severe vomiting which is often associated with the use of cis-platinum in the same condition may be acceptable to another.

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The ability to work, to earn money, and to be active outside the home is extremely important. Absence from work is one of the worst things that can happen to some women. Another woman may regard it as an opportunity to do something she had always wanted. Staying at home may be a disaster for one but a boon for another.

Family relationships, whether with a husband, son, daughter, or other relative, can be the most important thing in a woman's life. Another woman may not be so concerned about closeness to her family members. Such family ties may not always be loving ones. Some years ago a middle-aged man brought his wife into the hospital. She had had an exploratory laparotomy at another hospital for Stage III carcinoma of the ovary and had then been treated by abdominal radiation therapy. On admission she appeared to have extensive and almost terminal recurrent disease. It was clear, however, even from her few words, that she and her husband had a relationship in which she was the dominant figure and he the submissive one. We gave her chemotherapy—we were using Thiotepa at the time—and much to our surprise she had a remarkable remission which persisted for 6 months. As soon as she began to recover, the argumentative dominant-submissive relationship between her and her husband became obvious to everyone on the floor. And our perceptive social worker remarked that for this patient, perhaps, one part of the quality of her life lay in this antagonistic relationship.

The discovery of cancer or, indeed, of any serious disease adds a new and usually unpleasant dimension to an individual's concept of the good life. First, the symptoms of the disease itself, although often minor at the beginning, may affect various organs and functions. Kuebler-Ross[1] has pointed out that knowledge of approaching death results in a series of emotional responses—denial, anger, bargaining, depression, and

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resignation. Similar reactions occur when a diagnosis of cancer is first made, with possible substitution of the word "acceptance" for "resignation" (Table II).[2] These responses, it should be noted, do not necessarily occur consecutively or in the order listed. One may be predominant and more than one may occur at the same time. But whatever the reactions, they effect an underlying change in the individual's understanding of the quality of her life.

Primary treatment for cancer of the female genital tract alters function, activity, and family relationships in different but specific ways. The effect of surgical treatment depends on the type of cancer and the extent of the procedure. Relatively minor and temporary changes usually result from such procedures as a simple hysterectomy with or without removal of the ovaries or from local excision of a vulvar lesion. However, concern about unnecessary operations and about the possible ill-effects of removing the ovaries makes some women unduly apprehensive about oophorectomy even when it is done for cancer. Radical hysterectomy for Stage I cancer of the cervix is somewhat different. There are immediate changes in the urinary tract, consisting of bladder atony, and long-term changes in bladder sensation and micturition. Because of the shortness of the vagina there may be changes in the response to coitus, although the distensibility of that organ usually permits these to be surmounted. Radical vulvectomy as primary treatment for cancer of the vulva produces a major change in the sexual life of a woman particularly if sexual stimulation and activity has been largely confined to the pelvic area and the external genitalia. The notorious tendency of radical vulvectomy incisions to heal by secondary intention sometimes has the unexpected effect of making a woman dependent on her family for care when she had always cared for them in the past.

The effects of primary radiation therapy for cancer of the cervix or corpus uteri are often of a temporary nature. However, after the usual dose of external radiation many women note persistent changes in their intestinal tract, which alter food intake and bowel function. Years later they may say that there are certain foods that they cannot eat or that give them diarrhea. These effects are exaggerated if radiation is given to the para-aortic nodes or to the whole abdomen. Also, the shortening and stenosis of the upper vagina, primarily due to the internal application of radioactive sources, may adversely affect sexual relationships for the rest of a woman's life.

Until recently, chemotherapy has not been part of the primary treatment of gynecologic cancer. Now, however, single-drug chemotherapy, usually with an alkylating agent such as melphalan, is often employed after operation in all stages of ovarian cancer. Of more importance is multiple-drug chemotherapy. For example, such regimens as hexamethylmelamine, cyclophosphamide, methotrexate, and 5-fluorouracil[3] or doxorubicin and cyclophosphamide[4] have been used with considerable success and are being suggested as standard treatment after reductive surgery for carcinoma of the ovary, Stages III and IV. Chemotherapy affects the whole body and its side effects may involve many organ systems (Table III). It is easy to underestimate the cumulative impact of single-drug and especially multiple-drug chemotherapy on the whole patient.

Recurrent cancer places a much heavier burden on the patient's life. She may have disabling symptoms, and the knowledge that she still has disease despite her primary treatment recreates the denial, anger, bargaining, depression, and acceptance response. Also the treatment is likely to affect her more adversely. Secondary surgical treatment has typically been thought of as some type of exenteration. This results in a major change in the intestinal and urinary tracts and in the sexual apparatus. Recently, in persistent ovarian cancer, second-look procedures and operations for removal of bulky tumors or to relieve intestinal obstruction have been performed more frequently. All of these run the risk of affecting the patient's life by the formation of abdominal stomas such as colostomy, ileostomy, and mucous fistulas.

Table I. Basic components of life

1. Body functions
2. Work and activity
3. Family relationships

Table II. Reactions to diagnosis of cancer

1. Denial
2. Anger
3. Bargaining
4. Depression
5. Acceptance

Adapted from Kuebler-Ross.[1]

Table III. Complications of chemotherapy

1. *Gastrointestinal:*
   Nausea and vomiting
   Mucositis
2. *Hematologic:*
   Myelosuppression
3. *Dermatologic:*
   Alopecia, rash
4. Cardiac
5. Urinary tract

Table IV. Assessment to be used in patient management

1. Physiologic function
2. Psychosocial evaluation
3. Patient care conference
4. Treatment plan

Table V. Performance scale

Grade	*Performance*
0	Fully active
1	Strenuous activity restricted
2	Unable to work; capable of self-care
3	Mainly confined to bed or chair; limited self-care
4	Completely disabled

Table VI. Psychosocial assessment

1. Work
2. Activity
3. Recreation
4. Family relationships

If radiation is given for recurrent gynecologic cancer, it is often localized treatment which may disturb the patient very little. One exception is radiation to the perineum, whether by internal or external therapy. This can have a long-term effect on urinary and bowel function, as well as a continuing skin reaction.

Chemotherapy is commonly used for recurrent ovarian carcinoma, now more frequently for carcinoma of the corpus uteri, and occasionally for carcinoma of the cervix and vulva. The effects of chemotherapy mentioned previously are more than ever applicable in recurrent cancer.

It seems hardly appropriate to use the words "quality of life" in relation to the management of the patient terminally ill from cancer for whom all curative treatment has been exhausted. This has led some to use phrases such as "dying with dignity." Yet that is hardly appropriate, since it is life, even though it is finite, and its quality that are in question. With diminishing functions and activity, the quality of the remaining life is set at a different level from what a healthy person expects. Recognizing that vital physiologic functions are deteriorating and that work and even activity become difficult and eventually impossible, the patient's pain, the comfort of her surroundings, and her family relationships become increasingly important.

It is evident that some assessment of what a woman regards as important in her life is desirable if she is to be wisely counseled in the treatment of gynecologic cancer. Unfortunately, there is no good instrument for doing this. Experienced clinicians may say that such an assessment is a matter of clinical judgment, and I am sure that this is often the case with a sensitive and intuitive physician. However, the management of the patient with gynecologic cancer is often shared between many people, so that an organized approach to assessment of an individual's feelings about the quality of her life is important. There are four ways in which this can be done (Table IV). For some years performance scales have been used to assess function in the cancer patient and to evaluate the effects of therapy. One variety of this is shown in Table V. However, even more important is an attempt to evaluate the patient's feelings in regard to the physiologic functions of eating, urinating, defecating, sleeping, and sex. For a busy clinician who is taking her history this may be accomplished by asking how any disorder of these functions has affected her in the past; if it appears to have greatly disturbed her, then that function is important to the quality of her life. A psychosocial history can be obtained as part of the general history, but it is even more helpful to have a social worker see all patients, because additional relevant data can often be obtained in this way (Table VI). The advantage of a patient care conference is that information on what the patient considers important to her life may come from a variety of different sources. For many years I have held weekly patient care conferences attended by nurses, social workers, dietitians, home care nursing personnel, and physicians from different services. On occasion, a hospital chaplain has been a valuable asset to the group. Finally, it is helpful to indicate in some way on the patient's record, as part of her management plan, areas of concern in maintaining the quality of her life as she perceives it. Such an evaluation and management plan may require revision on several occasions during the patient's course.

The significance of the patient's quality of life, as she and her attendants understand it, varies according to whether she is to receive treatment for primary, recurrent, or terminal disease. In each category, the extent of the disease and its symptoms are important and must be balanced with the proposed treatment in regard to the overall effects on the patient's life. Although each patient with gynecologic cancer is an individual with her own special situation and problems, some guidelines can be drawn up.

1. In primary treatment, unless the cancer is too far advanced, the benefits of treatment, i.e., the likelihood of cure, generally outweigh the possible effects on the quality of the patient's life. This does not mean that the patient's concerns should be ignored. The task of all the health team concerned with her care is to help her to accept the functional changes that necessary treatment brings.

2. Recurrent cancer often involves more difficult decisions in regard to treatment, decisions in which the quality of life for the patient becomes crucially important. For example, an exenteration for recurrent carcinoma of the cervix is much more difficult therapy for a patient who is alone and has no near relatives than for a woman with an accepting, supportive family. Also, second-line chemotherapy for ovarian carcinoma with its attendant intestinal symptoms, hair loss, and weakness may be unacceptable to the patient, in comparison with the uncertain benefits offered.

3. The care of the terminal cancer patient may require the hardest decisions. Two questions have come under much discussion in recent years—the use of ordinary or extraordinary means to maintain life and the appropriateness of cardiopulmonary resuscitation. Granted that the relief of pain and provision of comfort are essential, it is often difficult to determine whether a given medication or treatment is ordinary or extraordinary. One of the hardest problems in the hospital setting, at least for me, is the continued use of intravenous fluids. The possible prolonged use of intravenous hyperalimentation further complicates this issue. From a philosophic and ethical point of view I think the term "reasonable or unreasonable" is more helpful than "ordinary or extraordinary."[5] On the practical side, the introduction and spread in this country of the hospice concept may make the transition period between life and death easier for the cancer patient.[6] The question of resuscitation offers many legal snags. It is very sensitively handled from a nonlegal point of view in a recent *New England Journal of Medicine* Editorial by Spencer.[7] He points out that in this area, where legal issues are unclear, where neither the patient nor the family can make a fully informed and objective decision, the physician is in a position in which he has to use his best judgment in the interests of all involved and "in which there is no escape from making such decisions."

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Ectopic pregnancy: Current clinical trends

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During the 16 year period ending in November, 1978, 191 cases of ectopic pregnancy were managed at the University of Virginia Hospital. The overall incidence was 1/126 deliveries but during the last 3 years of the study the incidence was 1/60 deliveries. Only 56 patients have had a subsequent conception. Thirteen have had a recurrent ectopic implantation. Only 36 women (23.7% of those available for follow-up) have had subsequent term pregnancies. Ectopic pregnancy continues to be a major gynecologic problem and the potential for subsequent fertility is poor.
(AM. J. OBSTET. GYNECOL. 134:870, 1979.)

THE DIAGNOSIS and managment of ectopic pregnancy continues to be a major problem in gynecology. The Committee on Maternal Health of the Medical Society of Virginia has determined that during the 8 year period from 1970 through 1977, 14 of the 31 maternal deaths (15.4%) attributable to maternal causes were related to complications of ectopic pregnancy. In addition, considerable evidence indicates that the incidence of this disorder may be increasing.[1-6] There is remarkable uniformity in the reported potential for successful subsequent pregnancy in these patients. The outlook is generally bleak in that less than half are likely to conceive again and only about one third can expect to produce a living child.[2, 4, 7-18]

In 1961, Thornton and associates[19] reviewed 89 cases of ectopic pregnancy managed at the University of Virginia Hospital. The purpose of this report is to present an additional 16 years' experience with this problem at the same institution and to review some of the current clinical trends with particular emphasis on available evidence regarding subsequent fertility.

Material and methods

Between July 1, 1962, and November 1, 1978, there were 23,987 deliveries at the University of Virginia Hospital. During this period, 191 ectopic pregnancies were treated in 178 women, an incidence of 0.80% or 1/126 deliveries. However, during the most recent 10 years of this study, the incidence has increased to 1.12% or 1 per 90 deliveries, and since 1975 there has been one ectopic pregnancy for every 60 deliveries (1.69%).

An intrauterine contraceptive device (IUD) was in place at the time of ectopic implantation in 20 cases (10.5%).

In 36 cases there had been no previous pregnancies and in 48 there had been only one prior pregnancy. However, in 107 (56%) pregnancy had occurred two or more times before (Table I). Among the IUD wearers, 75% had more than 1 prior pregnancy.

The majority of information included in this report was obtained from retrospective analysis of hospital records, operating room records, and pathology files. Of the 178 patients under consideration recent documentation of their subsequent medical history was available in 123. In an effort to extend the follow-up in the others, a questionnaire primarily directed toward establishing subsequent fertility was sent to 55 women. Twenty-six of these were not returned. Thus, adequate follow-up is limited to 152 patients.

Results

Menstrual history (Table II). In most cases (53.4%) patients described a normal menstrual period 4 to 8 weeks prior to admission. However, in 20.4% (including 30% of those wearing an IUD) there was no history of a missed period. In 60 (31.4%) cases there was no vaginal bleeding or "spotting" since the most recent

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period and there was no difference in the incidence of this symptom among the IUD users.

Pain. Lower abdominal or pelvic pain was present in 189 cases and in 84 (44%) was less than 24 hours in duration. In 55 cases (28.8%) pain had been present for 1 to 7 days, and in 50 (26.2%) pain had existed for more than 1 week. The IUD group did not differ from the other patients with regard to either the incidence of pain or its duration.

Physical findings (Table III). Adnexal tenderness was present in 180 cases (94.2%), and in 71 cases it was bilateral. A palpable adnexal mass was present in less than half of cases (43%) and in 16 of 82 (19.5%) was noted on the side opposite to that of the gestation. A palpable mass was slightly more common in the IUD group. An enlarged uterus was infrequent in both groups. Clinical shock, present in 33 cases (17.3%) overall, was twice as common in the IUD group (30%). None of the IUD patients presented with fever. Culdocentesis was performed in 42 cases and yielded nonclotting blood in all but three.

Laboratory tests. Preoperative hematocrits ranged from 15% to greater than 40% and correlated poorly with clinical shock. Of those patients with initial hematocrits less than 26%, 10 of 26 (38.5%) were in shock, but seven of 75 women (9.3%) with hematocrits greater than 35% were in clinical shock as well. Erythrocyte sedimentation rate and leukocyte counts were variable and of no diagnostic value. Pregnancy tests were performed in 70 cases and were positive in 50. Cervical mucus was examined in relatively few patients but showed ferning in 80%.

Operative findings. The anatomic distribution of the ectopic implantations is detailed in Table IV. There were three ovarian pregnancies in this series (all in IUD users) for an incidence of 1 in 63.7 ectopic pregnancies, or 1 in 6.7 ectopic pregnancies in women with an IUD.

The location of the corpus luteum was recorded in 84 of the 191 cases and was noted to be on the same side as the ectopic implantation in 57 and on the opposite side in 27. The corpus luteum was ipsilateral to the pregnancy in all nine cases in IUD users in whom this observation was made.

Twenty-eight patients had anatomic changes consistent with prior inflammatory disease in both the affected and contralateral fallopian tube.

Operative procedure. Immediate celiotomy was performed in 153 cases. Diagnostic laparoscopy preceded celiotomy in 27 cases and in another 11 cases diagnostic posterior colpotomy preceded celiotomy. Salpingectomy was performed in all cases of tubal implantation except one in which the products of conception were "stripped out." (This patient had a subsequent ectopic pregnancy in the same tube 3 months later.) Two of the ovarian pregnancies were managed by oophorectomy and one by partial oophorectomy.

Table I. Parity in 191 cases of ectopic pregnancy

Previous pregnancies (No.)	*Cases without IUDs (171)*		*Cases with IUDs (20)*		*Total cases (191)*	
	No.	*%*	*No.*	*%*	*No.*	*%*
0	34	20.5	2	10	36	19.4
1	45	26.3	3	15	48	25.1
2	32	18.7	7	35	39	20.4
3	23	13.4	1	5	24	12.6
≥4	37	21.6	7	35	44	23.0

Table II. Menstrual history in 191 cases of ectopic pregnancy

Interval since most recent menstrual period	*Cases without IUDs (171)*		*Cases with IUDs (20)*		*Total cases (191*	
	No.	*%*	*No.*	*%*	*No.*	*%*
≤4 wk.	33	19.3	6	30	39	20.4
4-8 wk.	91	53.2	11	55	102	53.4
8-12 wk.	29	17.0	3	15	32	16.8
>12 wk.	18	10.5	—		18	9.4

Table III. Physical findings in 191 cases of ectopic pregnancy

Findings	*Cases (191)*	
	No.	*%*
Adnexal tenderness:	180	94.2
Unilateral	109	
Bilateral	60	
Bilateral (with unilateral predominance)	11	
Peritoneal signs	146	76.4
Adnexal mass	82	43.0
Adnexal "fullness"	34	17.8
Clinical shock	33	17.3
Enlarged uterus	27	14.1
Fever (>37.8)	13	6.8

Course in hospital. One patient had a wound dehiscence, and two had febrile complications associated with coexistent pelvic inflammatory disease. The latter were the only two patients in this series with significant postoperative febrile morbidity.

There was one postoperative death. A 35-year-old multiparous woman was admitted with a mistaken diagnosis of incomplete abortion. Curettage was performed and she was discharged the next day. Four days later she returned with a ruptured ampullary ectopic pregnancy. Postoperatively, she developed pulmonary edema, congestive heart failure, and arrhythmia and died a few hours later. The cause of death was thought

Table IV. Operative findings in 191 cases of ectopic pregnancy

Site of implantation	Cases without IUDs (171)		Cases with IUDs (20)		Total cases (191)	
	No.	%	No.	%	No.	%
Right fallopian tube:	89	51.6	8	40	97	50.8
Ampulla	75	43.4	7	35	82	42.9
Isthmus	13	7.6	0	0	13	6.8
Interstitial	1	0.6	1	5	2	1.1
Left fallopian tube:	80	46.8	9	45	89	46.6
Ampulla	68	39.8	7	35	75	39.3
Isthmus	11	6.4	1	5	12	6.3
Interstitial	1	0.6	1	5	2	1.0
Ovary:	0	0	3	15	3	1.6
Right	0	0	2	10	2	1.0
Left	0	0	1	5	1	0.6
Other*	2	1.2	0	0	2	1.0

*One in a noncommunicating rudimentary uterine horn; one bilateral: left ampulla (acute) and right isthmus (chronic).

Table V. Subsequent fertility in 178 patients with ectopic pregnancy

Fertility status*	Patients (178)	
	No.*	%†
No subsequent pregnancy:	100	65.8
Contraception	20	13.2
Surgical sterilization	37	24.3
Unknown cause	41	27.0
Died	2	1.3
Subsequent pregnancy:	56	36.8
Term pregnancy	36‡	23.7
Recurrent ectopic pregnancy	13	8.6
Abortion	7	4.6
Lost to follow-up	26	—

*Four patients are included in two categories: One had therapeutic abortion followed by term pregnancy; two had a term pregnancy and a subsequent ectopic pregnancy; one had a spontaneous abortion followed by a term pregnancy with twins.

†Based on 152 patients available for follow-up.

‡These 36 women had 45 pregnancies including one set of twins.

to be related to aspiration. The pathology report from the curettage revealed only decidua.

Blood transfusions were not required in 73 cases (38.2%) including 11 of 20 (55%) in IUD wearers. One hundred twelve patients were given 1 to 6 U of blood and six others required more.

Subsequent fertility. The duration of follow-up is relatively short in 44 patients (2 years or less). Of 152 women available for review 65.8% have failed to achieve a subsequent pregnancy and in 27% there is no apparent reason.

In 56 cases (36.8% of those available to follow-up) there has been a subsequent conception, but only 36 (64.3% of those conceiving) have carried pregnancies to term. Ectopic pregnancy has recurred in 13 women (23.7% of those conceiving) and all of these have been subsequently infertile as a result of the second operative procedure.

Of the 43 patients who have not achieved a subsequent pregnancy (and who have not been sterilized or used contraception) one is now postmenopausal and two have died (one postoperatively and one of an unrelated illness). Forty remain involuntarily infertile.

Only five of the 36 women who were nulliparous at the time of the initial ectopic surgery have experienced a later term pregnancy (13.9%).

Comment

Although the overall incidence of ectopic pregnancy in this report (1/126 deliveries) is comparable to that in the earlier series from this clinic (1/149 deliveries), the trend in the most recent 3 years is markedly different (1/60 deliveries). It is possible that the increase in incidence may be, in part, apparent rather than real and related to a decrease in the number of normal term deliveries with no concomitant decrease in patients admitted for gynecologic emergencies. It has been suggested by one group that factors which may have been expected to increase the incidence of ectopic pregnancy in recent years include an increased incidence of gonorrhea as well as various family planning methods which reduce intrauterine pregnancy more effectively than ectopic pregnancy (induced abortion, IUDs, tubal sterilization). However, the same authors[17] cited a stable incidence of ectopic pregnancy in their clinic since 1950 (1 per 123 deliveries). A detailed epidemiologic study from England and Wales[1] indicates an increasing incidence in the late 1950's and a sharp increase since 1970. It is obvious that the incidence will vary with the population group under study, but the weight of the evidence appears to indicate an increase and in no case has any author presented evidence for a decrease.

The clinical features of the patients in this report with regard to demographic data, symptoms, and physical findings are not notably different from those described earlier by Thornton and associates and are consistent with generally accepted information.[17] Lower abdominal or pelvic pain is by far the most frequent symptom. Although almost half reported acute pain of less than 1 day's duration, a significant number (26.2%) had pain for more than a week, an observation which may reflect a persistent low index of suspicion for this disorder. Similarly the menstrual pattern was variable, with 20.4% of women reporting no abnormal menstrual history at all. The more common incidence of "normal" menstrual histories in IUD wearers may be

attributable in part to the tendency of such patients to consider vaginal bleeding and pelvic pain as "normal" side effects of the IUD and to the fact that some of these patients sought interruption of pregnancy before symptoms of ectopic gestation developed.

Adnexal tenderness and signs of peritoneal irritation were the most common physical findings. Although an adnexal mass was detected in 43% of cases, it was on the side opposite to that of the gestation in 19.5%, a finding consistent with that in our earlier series. This observation may be related to coincident pelvic inflammatory changes, accumulation of blood and clot in the pelvis, or palpation of a contralateral corpus luteum. The latter was present in 32% of patients in whom the location of the corpus luteum was noted and has been reported in 15% to 50% of cases in other reports.[18]

Accurate diagnosis and prompt management of ectopic pregnancy depend on clinical suspicion and careful assessment of symptoms and physical findings. Laboratory tests are of negligible value in diagnosis. Information obtained from diagnostic maneuvers such as culdocentesis and diagnostic ultrasound should be interpreted within the context of careful clinical assessment and must not be allowed to delay operative intervention if clinical suspicion exists. Diagnostic laparoscopy may be useful but is contraindicated if obvious clinical evidence of an abdominal emergency exists.

An association between ectopic pregnancy and the use of IUDs was recognized by Gräfenberg in 1929. A detailed analysis of this correlation by Lehfeldt and associates[6] in 1970 suggested that 4.3% of accidental pregnancies occurring in IUD users are likely to be ectopic and that one ectopic pregnancy will occur per 1,000 IUD users per year. It was further concluded that an IUD reduces uterine implantation far more effectively than it reduces either tubal or ovarian implantation. They and others[5, 18] point out that the IUD is probably not causal but is simply not protective against ectopic implantation in predisposed patients. Barron and associates[20] concluded that the overall incidence of ectopic pregnancy may be slightly lower in women using the IUD but that the relative risk in those women who conceive is (using Lehfeldt's data) increased 2.5-fold to ten-fold. Although this association is generally regarded as evidence of a mode of action of the IUD,[6, 18, 21] Weekes and Sutherst[22] pointed out that the relationship of the IUD and ectopic pregnancy may be indirect, in that IUD users are at increased risk of pelvic inflammatory disease. Soderstrom[23] has presented data indicating that 47% of women using the IUD who undergo laparoscopic sterilization have visual evidence of "salpingitis" (although cultures may be sterile).

Regardless of the exact role of the IUD, it is apparent that patients using the device are at risk and if pregnancy occurs it will be ectopic in 1 of 23 cases.[6] Thus a high index of suspicion is required especially in view of the frequency of lower abdominal pain and abnormal bleeding in these women. Seward and associates[24] have succinctly summarized the appropriate management of IUD wearers when pregnancy is confirmed. If the pregnancy is to be allowed to continue, careful examination and removal of the IUD are done, warning given regarding symptoms of ectopic pregnancy, and close follow-up provided until the pregnancy is established to be intrauterine. If therapeutic abortion is requested (or spontaneous abortion ensues), examination with anesthesia, culdocentesis, and careful examination of the tissue obtained from the uterus are recommended. We believe that frozen-section examination of curettage specimens is advisable in these cases. In the present series five patients (including the one maternal death) were found to have an ectopic pregnancy after an initial diagnosis of either spontaneous or induced abortion.

The occurrence of three ovarian pregnancies among the IUD group in this series (15%) is consistent with that of other reports.[21] This is presumably related to the relative ineffectiveness of the device in preventing ovarian implantation as compared with both tubal and intrauterine implantation.[6] Coustan and colleagues[25] suggested that diagnostic laparoscopy may be misleading in cases of suspected ectopic gestation if ovarian pregnancy is not seriously considered, as the superficial appearance may resemble that of an ovarian cyst.

Women who have experienced an ectopic pregnancy have a higher subsequent incidence of persistent infertility, recurrent ectopic pregnancy, and pregnancy wastage. Swolin and Fall[4] reviewed the literature in 1972 and found that 38% to 70% of patients were infertile after surgery, 25% to 69% had a subsequent normal intrauterine pregnancy, and recurrent ectopic pregnancy occurred in 4% to 25%. These figures will obviously be influenced by differences in the population under study, desire for subsequent pregnancy, coexistent pelvic disease, type of operation performed, other fertility factors, and duration of follow-up. Regardless of such differences the fact remains that no more than half are likely to conceive again, only one third will have a successful term pregnancy, and the risk of another ectopic gestation is increased thirtyfold to fiftyfold.[2-4, 7-10, 11-13, 14-15, 18] The results of the current study are in accordance with these rather discouraging observations and there is little evidence in

the recent literature to suggest any improvement in he outlook for future fertility.

Jeffcoate's[26] proposal in 1955 that concomitant ipsilateral oophorectomy be considered in women subjected to salpingectomy in order that the remaining tube be provided with as many ova as possible has been both supported[9] and refuted.[7, 10, 16] Available evidence does not clearly establish an advantage in removing a normal ovary and it appears that preservation of such ovaries is indicated in these women who already have low fertility potential.

The current availability of improved techniques for tubal reconstructive surgery may provide better opportunities for successful subsequent fertility in the future. Timonen and Nieminen[8] found similar rates of successful pregnancy after radical (anything more than tubal reconstruction) and conservative surgery but the recurrence rate of ectopic pregnancy was greater in the conservatively treated group. Others[16] have found no difference. Despite the clear risk of recurrent ectopic pregnancy it must be re-emphasized that successful pregnancies do occur in about one third of women and that this is a highly significant proportion when it is recognized that many have not had a prior successful gestation. We should be realistic about the prospects for future pregnancy but is is possible that too many salvageable tubes are sacrificed because of defeatism and unwillingness to assume reasonable risks. Bender[9] suggested that the uninvolved tube should be carefully inspected before the affected tube is excised so that salpingotomy may be considered if the uninvolved tube is rudimentary or hopelessly damaged. He and others[10, 12] stressed the importance of removing clot and blood (in an effort to decrease the incidence of adhesions and infection) as well as the use of prophylactic antibiotics. McElin and Iffy[18] in a recent detailed review presented cogent arguments in favor of such measures and further recommended that intraoperative hydrotubation as well as immediate postoperative hysterosalpingography be considered. They concluded that any reasonable management concept which might enhance future fertility is desirable.

The current clinical trends in ectopic pregnancy are depressingly similar to those of earlier reports. Women still die of this disease and despite the availability of appropriate antibiotic treatment for one of its major recognized predisposing conditions (pelvic inflammatory disease) the incidence is apparently not decreasing. A high index of suspicion is necessary, especially in women with prior pelvic infections or ectopic pregnancies, those wearing an IUD, and those with histories of primary infertility. An understanding of the implications regarding future fertility should be provided to the patient. Serious consideration should be given to management methods that may offer better potential for future reproduction. Aggressive extirpative surgery may not be required in all cases and skilled application of the principles of tubal reconstructive surgery may offer a brighter fertility future to selected women.

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Discussion

DR. LOUIS KEFFER (Official Guest), Newport News, Virginia. It is refreshing to hear a paper dealing with a problem that all of us face in our day-to-day practice. Extrauterine pregnancy not only is not declining in frequency, as many medical problems are, but is actually on the increase, when expressed as a ratio of ectopic pregnancies per delivery. In the authors' series, over a 16 year period, the incidence was one ectopic pregnancy for each 126 deliveries. In the more recent years of the series it has been 1 in 60. The incidence in my hospital is presently 1 in 80. When Dr. Ware wrote a paper on this subject approximately 30 years ago, the figure was 1 in 300.

The increased incidence, at least as related to one factor, the IUD, may be more apparent than real. The relatively large number of ectopic pregnancies among IUD users, due to selective suppression of intrauterine but not extrauterine pregnancies, introduces an interesting concept. This same selectivity is true in regard to elective abortions.

The tremendous increase in gonococcal infections, particularly in teenagers, has produced and undoubtedly will produce a very real rise in the number of ectopic pregnancies.

In the authors' series 20.4% of the patients reported no missed menstrual periods. Perhaps it is more to the point that 68.6% did report missed periods. It is possible that a very persistent history taker could raise that percentage even higher. Many patients who at first deny missed menses will later admit that the last one or two were not altogether normal.

Pain is virtually always the most prominent feature and nearly always the symptom that first causes the patient to seek medical assistance. The laboratory is usually of little value in making a correct diagnosis. An exception is when the rupture is not so explosive and the blood loss not as sudden and massive as in the classical textbook example of ectopic pregnancy. In cases where the blood loss is gradual, serial hematocrit and hemoglobin determinations are of great value. Pregnancy tests may well be misleading. A positive test may occur with intrauterine pregnancy and hemoperitoneum due to a bleeding corpus luteum, and a negative test may be found in an ectopic pregnancy with a conceptus no longer living.

Invasive diagnostic techniques should be limited to those cases not easily diagnosed by history and physical findings. Laparoscopy is definitely preferable to culdocentesis. In the latter, both false positive and false negative findings are frequent. The laparoscope, however, not only confirms the presence of hemoperitoneum but usually identifies its source as well.

The prevalence of low fertility both before and after an ectopic pregnancy and the risk of a repeat extopic gestation has long been known and is well documented by the paper presented.

In a small series of 27 ectopic pregnancies, during 1978, at Riverside Hospital, 18, or 67%, had no or one previous delivery. The age distribution was predictable. Fifteen patients were between 20 and 24 years of age. Nine were between 25 and 30, and only three were between 31 and 40. Fifteen of the 27 patients required no transfusions and of those who did 11 patients needed 1 to 4 U. All of our patients reported missed or abnormal menses. Twenty-two (all but five) had missed only one or two menses. Three of the 27 were IUD users (11%). One had had a laparoscopic sterilization by cautery. One patient had endometriosis, and one had active gonorrhea, diagnosed by cervical culture

The authors' paper re-emphasized the importance of early diagnosis and prompt surgical intervention. It also reminds us of the importance of having a high degree of suspicion, particularly with women at risk, namely, those with a history of infertility, IUD use, pelvic inflammatory disease, and prior ectopic pregnancy. This paper also reminds us that although we will not be able to lower the incidence of ectopics gestation we can surely decrease the morbidity and mortality rates by diagnostic acumen and surgical skill.

DR. JAMES EDWIN CLEMENT, Greenville, North Carolina. Dr. Kitchin and his associates have again brought to our attention the importance of an entity which is not only protean but common enough to cause loss of sleep by all physicians who care for young women.

The clear-cut case of "ectopic" pregnancy still exists. In addition, Dr. Kitchin has pointed out the increased incidence of the problem in the "uncharacteristic" patient, who, as well, must be carefully scrutinized when she comes in with a history of pain, spotting, and a missed menstrual period, with a pelvic mass. The reported increased incidence of 1 in 60 pregnancies in the last three years at the University of Virginia should alert every physician who cares for women, because, as it has been pointed out, ectopic pregnancies still account for 50% of all maternally related maternal deaths in the United States, with less than 50% of those who survive ever conceiving again; of these, 23% will be ectopic pregnancies. Perhaps as important as any fact which he has brought to our attention, however, is the fact that in this study only five of 37 nulliparous patients ever became pregnant again.

The review of such a report from a university hospital allows one to review one's own situation and, hopefully, by review to improve upon patient care.

In looking over the statistics of our own community hospital for the years 1967 to 1977, we have found, in a hospital service of comparable size, that the occurrence rate has been 1:164 in the first five years of our review and 1:120 in the last six years. We have also noted a decrease in incidence to 1:187 in 1977. It is interesting to note that in our county, with a 46% black population, there was an almost equal distribution between the

races. The surgical approach at laparotomy was similar, with 55% having salpingectomy and 20% to 25% having elective bilateral tubal ligation. A similar number received transfusion (44% compared to 38% at the University of Virginia). Nontubal (ovarian, cornual, and abdominal) pregnancies occurred in three of 104 of the patients in our hospital, while at the University of Virginia one of 63 ectopic pregnancies was ovarian.

The difficulty in classical diagnosis has been compounded by the IUD-ectopic question. In the early years of observation of this entity, there undoubtedly existed the problem of disbelief that extrauterine (or intrauterine) pregnancy often occurred with an IUD. Surely the fact that 17% of the University of Virginia group with IUDs–ectopic pregnancies were in shock was due to this factor. In the early years of recognition of this problem (10 to 15 years ago), I kept a careful personal account of each patient with an IUD who developed an ectopic pregnancy and could account for practically each one from memory. But recently the occurrences have been commonplace. I agree with the report of Dr. Kitchin and colleagues that probably one of 23 pregnancies associated with an IUD is ectopic.

The use of pregnancy tests, which were done in 37% of the University of Virginia patients (and were positive in 50 of 70), has also many times clouded the picture and caused delay. Perhaps the newer, more refined evaluations of human chorionic gonadotropin will be more reliable and useful when they become more accessible and when more physicians use them.

Abdominal pain in young women, particularly in patients with pelvic inflamation, IUD's, and endometriosis, is very common and cannot often in itself be very helpful in diagnosis. All but two of the patients reported in the University of Virginia study had this symptom. In addition, as every gynecologist knows, a pelvic mass in a patient with an acute process is very hard and often impossible to palpate, particularly in young girls who are prime candidates for extrauterine gestation.

So I will make a plea for the early use of culdocentesis in all patients in whom the diagnosis of ectopic pregnancy is suspected. While it is true that diagnostic laparoscopy is helpful in patients with so-called "mild" ectopic pregnancy, as is ultrasound, a positive culdocentesis with a syringe full of nonclotting blood gives information which cannot be denied. It can be obtained in minutes and before the patient becomes involved in the hospital delay-mill. Certainly an unyielding tap is not informative. But every gynecologist (and especially those in training) should be prepared not only to perform it in every patient, not in shock, who has the characteristic pelvic-abdominal findings which make one suspect ectopic pregnancy.

Bilateral Paget's disease of the nipple: Case report

W. RICHARD ANDERSON, M.D.
St. Petersburg, Florida

Paget's disease of the breast accounts for 1% to 4.1% of all cancers; however, bilateral Paget's disease is extremely rare. A case of bilateral Paget's disease is presented and treatment is described. (AM. J. OBSTET. GYNECOL. 134:877, 1979.)

DIAGNOSIS OF LESIONS of the breast has become a major responsibility of the gynecologist. Although Paget's disease of the breast is not rare, accounting for 1% to 4.1% of all cancers, bilateral Paget's disease is extremely rare. In the literature of the past ten years I found no cases of bilateral Paget's disease. In a personal communication, Henry J. Norris, of the Air Force Institute of Pathology, confirmed the rarity of this disease. Lever[4] stated in *Histopathology of the Skin* that the lesion is always unilateral. This case is reported to remind the gynecologist of the clinical presentation of Paget's disease and to add to the literature a case of bilateral Paget's disease of the nipple.

Case presentation

A 53-year-old woman, gravida 2, para 2, was seen for her yearly physical examination; she had no complaints. On examination a scaly, pinkish lesion was found on both nipples of the breasts. With local analgesia and using a Keyes punch biopsy a small portion of the right nipple was taken. The impression was Paget's disease of the right nipple but since it appeared to be bilateral the pathologist requested a larger sample. A wedge of both nipples was taken following general anesthesia. Again, our pathologist felt that this was Paget's disease, but since it was bilateral he referred the slides to the Armed Forces Institute of Pathology, which confirmed the diagnosis of Paget's disease of the nipple. No masses could be palpated and xeromammography proved to be negative. Bilateral modified radical mastectomy was performed. A small focus of intraductal carcinoma was found deep within the left breast, but despite repeated serial sections of the right breast no further malignancy was observed. All nodes from both the right and left axilla were negative. The patient did well postoperatively and was free of obvious disease when last seen in September, 1978.

Comment

Paget's disease of the nipple occurs in middle-aged women. In a series of 159 cases reported by Kister and Haagensen,[2] the range in age was 26 to 81 with a mean age of 54. The lesion is characterized by an inflammatory response which has the appearance of chronic eczema. There is usually a sharply demarcated area around the nipple, involving all or part of the nipple and areola. The superficial epithelium may be denuded. It is moist and soft and may be covered with a crust or a scab. In 10% of cases there is no visible clinical lesion.

Differential diagnosis of Paget's disease of the nipple should include: (1) benign intraductal papillomas, which extend out onto the surface of the nipple; (2) benign dermatologic lesions; (3) secondary invasion of the nipple by carcinoma elsewhere. When benign intraductal papillomas are present there is a firm nodule which can be easily felt in the nipple, and there is oozing of serum and blood, not a true discharge. In benign dermatologic lesions the spread of the disease is usually rapid and involves not only the areola but the surrounding skin. In invasive cancer of the nipple the contour of the breast is usually destroyed.

In 50% of cases no palpable lesion is present. In patients with a palpable lesion two thirds will have positive axillary lymph nodes. One third of the patients without palpable lesions will have positive lymph nodes. There have been several reports of positive lymph nodes when no breast tumor was found in the surgical specimen.

Few cancers are so easily seen and give the opportunity for easy biopsy and diagnosis. Any lesion of the nipple should be biopsied prior to treatment. The delay in making the diagnosis many times is 15 to 18 months. With a high index of suspicion the diagnosis of

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Paget's disease of the nipple can be made early and treatment instituted. Biopsy is the only way of establishing a diagnosis. Biopsy of the nipple can be done very simply as an office procedure with local anesthesia and a dermal Keye's punch biopsy.

Treatment of choice is modified radical mastectomy. Since there have been reports of positive nodes without a palpable lesion and without presence of a carcinoma deep within the breast, simple mastectomy is insufficient treatment. Kister and Haagensen[2] reported a 10 year survival rate of 79% with no axillary spread. There was a 29% survival rate in women with axillary spread. Other series gave similar cure rates.

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Identical twins with twisted benign cystic teratoma of the ovary

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Lumberton, North Carolina

THE TWO CASES reported here represent, for your consideration, some aspects of the diagnosis of complications of benign cystic teratoma of the ovary, the origin of benign cystic teratoma of the ovary, and the treatment thereof.

Case reports

Case 1. T. L., a 24-year-old, Lumbee Indian, nulliparous woman, presented with a 2 week history of lower abdominal pain. She had been treated elsewhere for pelvic inflammatory disease with antibiotics and no improvement. Surgery had been recommended for her "infection." When initially seen, she was afebrile. Physical findings were limited to the abdomen and pelvis. The abdomen was slightly protuberant with normal peristalsis and minimal spasm and guarding. There was some low abdominal tenderness without rebound. The uterus was of normal size. A left adnexal, irregular cystic mass extended from the anterior surface of the uterus to the left pelvic side wall. A right adnexal, exquisitely tender mass extended posteriorly to the uterus and into the cul-de-sac. Outpatient therapy of suspected pelvic inflammatory disease was continued with tetracycline. One week later, she was essentially asymptomatic and had been afebrile throughout the past week. Examination revealed the left adnexal mass to be mobile. The right mass was less tender but was fixed. One week subsequent to this, the left mass was interpreted as being completely mobile and cystic. Pelvic laparotomy for pelvic inflammatory disease or twisted ovarian cyst was performed on November 25, 1964, and revealed a twisted, infarcted, hemorrhagic, 12 cm, benign cystic teratoma of the right ovary. The left ovary was quite large and contained five separate benign cystic teratomas measuring from 1 to 8 cm in diameter. The right adnexa were removed, and multiple cystectomies were performed on the left ovary with preservation of ovarian tissue. In 1969, a 6 cm cystic teratoma of the ovary was removed. In 1971, at the time of elective repeat cesarean section, a 1.5 by 1.5 cm benign cystic teratoma of the ovary was removed, for a total of seven benign cystic teratomas of the left ovary. The patient continues to be examined at regular intervals and is completely asymptomatic.

Case 2. V. E., a 25-year-old twin sister of T. L., gravida 4, para 4. was seen in 1966, when she was acutely ill with a chief complaint of the sudden onset of rather severe, right–lower quadrant abdominal pain which was becoming progressively worse. Abdominal examination revealed low abdominal tenderness without rebound or referred tenderness. Bowel sounds were normal. The uterus was anterior, of normal size, and freely movable. There was some pain referable to the right lower quadrant upon manipulation, and there was a questionable "doughy" mass on the right. The left adnexa were not delineated. Antibiotics were administered. Twelve hours later, examination revealed a 6 to 8 cm cyst on the right ovary. An irregular mass was also palpated on the left ovary. Laparotomy revealed a 14 cm, twisted, infarcted, hemorrhagic, benign cystic teratoma of the right ovary. The left ovary was four times normal size with three benign cystic teratomas. The right adnexa were removed, and left ovarian cystectomies were performed with preservation of ovarian tissue.

Comment

Review of the literature failed to demonstrate the incidence of benign cystic teratomas in twins to be different than that in offspring of single births. The etiology of benign cystic teratomas, which is discussed below, lends only speculative reasons as to why they occur.

Benign cystic teratomas of the ovaries are the most common of all ovarian neoplasms, representing approximately 20% of all ovarian neoplasia.[1] Various authors[1, 2] have stated that from 12% to 25% occur bilaterally. Many neoplasms of the ovary are so small they are not recognized unless the ovary is bisected.

Today, the etiology of benign cystic teratomas remains speculative. One theory is that totipotent cells

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(blastomeres) are segregated at an early state in the development of the morula. Such cells would be capable of forming derivatives of all three germinal cell layers. Why such cells concentrate in the ovary is difficult to explain.

A more widely accepted theory is that of parthenogenesis or asexual development. The spark that stimulates such imperfect development is unknown. The first case presented (Patient T. L.) promotes speculation of a continuing stimulus for such development.

The most common complication of benign cystic teratoma of the ovary is torsion, which may occur as often as 15% of the time.[3] The mechanism of torsion is unknown. Other complications include rupture of the benign cystic teratoma, malignant degeneration, and adherence to and erosion into the intestinal tract and bladder.[4]

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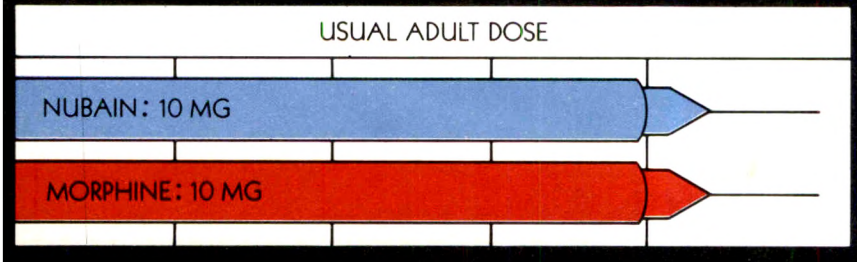


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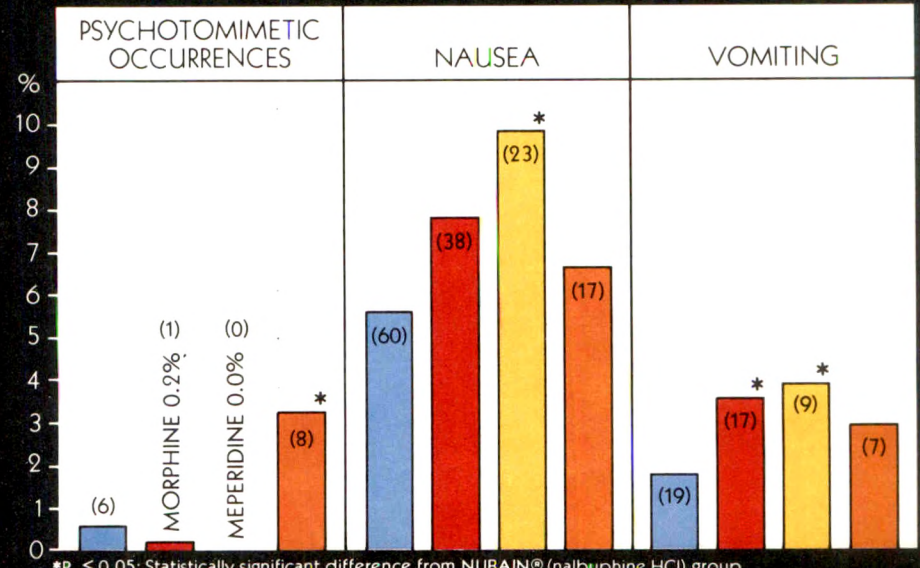
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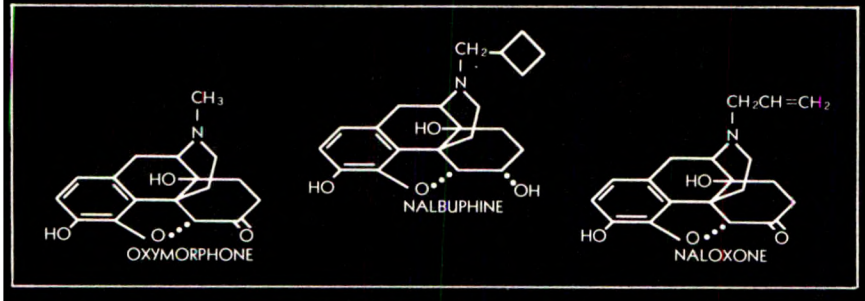
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NUBAIN requires no special storage or additional paperwork beyond your normal order or prescription.

The unique properties of NUBAIN may be found in its molecular structure.



Certain substances, such as NARCAN® (naloxone HCl), counteract or antagonize the effects and side effects of potent narcotics, such as morphine or NUMORPHAN® (oxymorphone HCl). NUBAIN was designed to incorporate important molecular features of the antagonist NARCAN and the potent analgesic NUMORPHAN, resulting in a drug with strong analgesia but limited abuse potential.

And a lower respiratory effect

At dosages of 10 mg/70 kg, NUBAIN causes respiratory depression comparable to that of morphine. In contrast to morphine, higher doses of NUBAIN do not increase respiratory depression appreciably (see Precautions).

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Please see complete prescribing information on last page of this advertisement.



A clinical summary:

27 investigations evaluated more than 1,000 medical and surgical patients in regard to the effect of NUBAIN upon acute or chronic pain. Among these studies are the following, which highlight important areas of analgesic use:

- ORTHOPEDICS—this study encompassed 52 patients and compared NUBAIN to meperidine. Treatment varied from 1 to 40 days. NUBAIN was found to deliver satisfactory analgesia with no overt evidence of physical tolerance.
- CANCER—this study encompassed 37 patients treated for 1 to 186 days. Many of the patients stabilized on I.M. NUBAIN received dosages every 6-8 hours.
- OBSTETRICS—four double-blind studies were conducted encompassing 159 patients in labor. I.M. NUBAIN was compared to I.M. meperidine. Analgesically, both drugs were deemed similar (10-15 mg NUBAIN equal to 75-113 mg meperidine). Neonates did equally well on both drugs, but there is a possibility that either drug can produce depressive effects in the fetus or neonate. Mothers treated with NUBAIN had fewer side effects, and hospital personnel liked NUBAIN.
- Please see full prescribing information, including a complete discussion of adverse reactions, on following page.

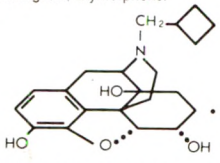
NUBAIN® (nalbuphine HCl)

Analgesia comparable to morphine, with important differences

new NUBAIN®
nalbuphine HCl

DESCRIPTION

NUBAIN (nalbuphine hydrochloride) is a synthetic narcotic agonist-antagonist analgesic of the phenanthrene series. It is chemically related to both the widely used narcotic antagonist, naloxone, and the potent narcotic analgesic, oxymorphone.



NALBUPHINE HYDROCHLORIDE

(-)-17-(cyclobutylmethyl)-4, 5α-epoxy-morphinan-3, 6α, 14-triol, hydrochloride • HCl

Each ml of the injectable aqueous solution of NUBAIN contains 10 mg of nalbuphine hydrochloride.

ACTIONS

NUBAIN is a potent analgesic. Its analgesic potency is essentially equivalent to that of morphine on a milligram basis.

Its onset of action occurs within 2 to 3 minutes after intravenous administration, and in less than 15 minutes following subcutaneous or intramuscular injection. The plasma half-life of nalbuphine is 5 hours and in clinical studies the duration of analgesic activity has been reported to range from 3 to 6 hours.

The narcotic antagonist activity of NUBAIN is one-fourth as potent as nalorphine and 10 times that of pentazocine.

INDICATIONS

For the relief of moderate to severe pain. NUBAIN can also be used for preoperative analgesia, as a supplement to surgical anesthesia, and for obstetrical analgesia during labor.

CONTRAINDICATIONS

NUBAIN should not be administered to patients who are hypersensitive to it.

WARNINGS

Drug Dependence NUBAIN has been shown to have a low abuse potential which is approximate to that of pentazocine. When compared with drugs which are not mixed agonist-antagonists, it has been reported that nalbuphine's potential for abuse would be less than that of codeine and propoxyphene. Psychological and physical dependence and tolerance may follow the abuse or misuse of nalbuphine. Therefore, caution should be observed in prescribing it for emotionally unstable patients, or for individuals with a history of narcotic abuse. Such patients should be closely supervised when long-term therapy is contemplated.

Care should be taken to avoid increases in dosage or frequency of administration which in susceptible individuals might result in physical dependence.

Abrupt discontinuation of NUBAIN following prolonged use has been followed by symptoms of narcotic withdrawal, i.e., abdominal cramps, nausea and vomiting, rhinorrhea, lacrimation, restlessness, anxiety, elevated temperature and piloerection.

Use in Ambulatory Patients NUBAIN may impair the mental or physical abilities required for the performance of potentially dangerous tasks such as driving a car or operating machinery. Therefore, NUBAIN should be administered with caution to ambulatory patients who should be warned to avoid such hazards.

Use in Emergency Procedures Maintain patient under observation until recovered from NUBAIN effects that would affect driving or other potentially dangerous tasks.

Use in Children Clinical experience to support administration to patients under 18 years is not available at present.

Use in Pregnancy (other than labor) Safe use of NUBAIN in pregnancy has not been established. Although animal reproductive studies have not revealed teratogenic or embryotoxic effects, nalbuphine should only be administered to pregnant women when, in the judgement of the physician, the potential benefits outweigh the possible hazards.

Use During Labor and Delivery NUBAIN can produce respiratory depression in the neonate. It should be used with caution in women delivering premature infants.

Head Injury and Increased Intracranial Pressure The possible respiratory depressant effects and the potential of potent analgesics to elevate cerebrospinal fluid pressure (resulting from vasodilation following CO_2 retention) may be markedly exaggerated in the presence of head injury, intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, potent analgesics can produce effects which may obscure the clinical course of patients with head injuries. Therefore, NUBAIN should be used in these circumstances only when essential, and then should be administered with extreme caution.

Interaction With Other Central Nervous System Depressants Although NUBAIN possesses narcotic antagonist activity, there is evidence that in nondependent patients it will not antagonize a narcotic analgesic administered just before, concurrently, or just after an injection of NUBAIN. Therefore, patients receiving a narcotic analgesic, general anesthetics, phenothiazines, or other tranquilizers, sedatives, hypnotics, or other CNS depressants (including alcohol) concomitantly with NUBAIN may exhibit an additive effect. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

PRECAUTIONS

Impaired Respiration At the usual adult dose of 10 mg/70 kg, NUBAIN causes some respiratory depression approximately equal to that produced by equal doses of morphine. However, in contrast to morphine, respiratory depression is not appreciably increased with higher doses of NUBAIN. Respiratory depression induced by NUBAIN can be reversed by NARCAN® (naloxone hydrochloride) when indicated. NUBAIN should be administered with caution at low doses to patients with impaired respiration (e.g., from other medication, uremia, bronchial asthma, severe infection, cyanosis or respiratory obstructions).

Impaired Renal or Hepatic Function Because NUBAIN is metabolized in the liver and excreted by the kidneys, patients with renal or liver dysfunction may overreact to customary doses. Therefore, in these individuals, NUBAIN should be used with caution and administered in reduced amounts.

Myocardial Infarction As with all potent analgesics, NUBAIN should be used with caution in patients with myocardial infarction who have nausea or vomiting.

Biliary Tract Surgery As with all narcotic analgesics, NUBAIN should be used with caution in patients about to undergo surgery of the biliary tract since it may cause spasm of the sphincter of Oddi.

ADVERSE REACTIONS

The most frequent adverse reaction in 1066 patients treated with NUBAIN is sedation (381, 36%). Less frequent reactions are: sweaty/clammy (99, 9%), nausea/vomiting (68, 6%), dizziness/vertigo (58, 5%), dry mouth (44, 4%), and headache (27, 3%).

Other adverse reactions which may occur (reported incidence of 1% or less) are:

CNS Effects nervousness, depression, restlessness, crying, euphoria, floating, hostility, unusual dreams, confusion, faintness, hallucinations, dysphoria, feeling of heaviness, numbness, tingling, unreality. The incidence of psychotomimetic effects, such as unreality, depersonalization, delusions, dysphoria and hallucinations has been shown to be less than that which occurs with pentazocine.

Cardiovascular Hypertension, hypotension, bradycardia, tachycardia.

Gastrointestinal Cramps, dyspepsia, bitter taste.

Respiration Depression, dyspnea, asthma.

Dermatological Itching, burning, urticaria.

Miscellaneous Speech difficulty, urinary urgency, blurred vision, flushing and warmth.

DOSAGE AND ADMINISTRATION

The usual recommended adult dose is 10 mg for a 70 kg individual, administered subcutaneously, intramuscularly or intravenously; this dose may be repeated every 3 to 6 hours as necessary. Dosage should be adjusted according to the severity of the pain, physical status of the patient, and other medications which the patient may be receiving. (See Interaction with Other Central Nervous System Depressants under WARNINGS.) In non-tolerant individuals, the recommended single maximum dose is 20 mg, with a maximum total daily dose of 160 mg.

Patients Dependent on Narcotics Patients who have been taking narcotics chronically may experience withdrawal symptoms upon the administration of NUBAIN. If unduly troublesome, narcotic withdrawal symptoms can be controlled by the slow intravenous administration of small increments of morphine, until relief occurs. If the previous analgesic was morphine, meperidine, codeine, or other narcotic with similar duration of activity, one-fourth of the anticipated dose of NUBAIN can be administered initially and the patient observed for signs of withdrawal, i.e., abdominal cramps, nausea and vomiting, lacrimation, rhinorrhea, anxiety, restlessness, elevation of temperature or piloerection. If untoward symptoms do not occur, progressively larger doses may be tried at appropriate intervals until the desired level of analgesia is obtained with NUBAIN.

Management of Overdosage The immediate intravenous administration of NARCAN® (naloxone hydrochloride) is a specific antidote. Oxygen, intravenous fluids, vasopressors and other supportive measures should be used as indicated.

The administration of single doses of 72 mg of NUBAIN intramuscularly to eight normal subjects has been reported to have resulted primarily in symptoms of sleepiness and mild dysphoria.

HOW SUPPLIED

NUBAIN® (nalbuphine hydrochloride) injection for intramuscular, subcutaneous, or intravenous use (10 mg/ml) is available in:

NDC #0056-0385 10 mg/ml, 1 ml ampuls (box of 10)
NDC #0056-0384 10 mg/ml, 2 ml ampuls (box of 10)
NDC #0056-0386 10 mg/ml, 10 ml vials

Each ml contains 10 mg nalbuphine hydrochloride, 0.1% sodium chloride, 0.94% sodium citrate, 1.26% citric acid anhydrous, 0.1% sodium metabisulfite, and 0.2% of a 9:1 mixture of methylparaben and propylparaben as preservative; pH is adjusted with hydrochloric acid.

6094-1

Rev. March 1979

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Bicornuate uterus and partial atresia of the fallopian tube

MARTIN FARBER, M.D.
GEORGE W. MITCHELL, JR., M.D.
Boston, Massachusetts

Partial atresia of the fallopian tube was discovered in two patients with double uteri of the bicornuate variety. The abnormal tube in each case was ipsilateral to a noncommunicating, nonfunctioning, rudimentary uterine horn. A normal fimbriated end led to a short, patent ampullary portion that ended blindly in the mesosalpinx. Realization of the potential for the coexistence of congenital malformation of the fallopian tubes with various uterine malformations suggests that extreme caution be exercised during adnexal surgery in patients with anomalous development of the müllerian ducts. (AM. J. OBSTET. GYNECOL. 134:881, 1979.)

THE EMBRYOLOGIC EVENTS that result in the normal development of the fallopian tubes, uterus, cervix, and vagina in the woman are subtle and complex; although the past 50 years have yielded numerous descriptive treatises[1–3] no one is universally accepted.[4] The potential for varieties of malformations of the genital ducts is infinite but experientially certain patterns have emerged to permit their classification and to facilitate their diagnosis. Congenital anomalies of the müllerian (paramesonephric) ducts may be functionally categorized in those patients who present with: (1) amenorrhea, (2) amenorrhea and cryptomenorrhea, (3) cryptomenorrhea and menstrual egress per vagina, or (4) reproductive failure.[5] Alternatively these anomalies may be etiologically classified as those due to (1) complete unilateral failure of müllerian duct development, (2) partial unilateral or bilateral müllerian duct failure, or (3) failure of fusion of the müllerian ducts.[6] Often several etiologies must be invoked to explain a single functional result.

Anomalies of the paramesonephric ducts have been estimated to occur in 1/500 to 1/2,000 women.[7] Those resulting from unilateral partial müllerian duct maldevelopment or unilateral partial maldevelopment together with failure of fusion of the ducts are very unusual. Exemplary of the former are isolated reports of anomalous fallopian tube development. Unilateral duplication of the tube[8] and unilateral tubal ectopia have each been reported once.[9] In the case report of unilateral ovarian and fallopian tube absence with a stone in the cul-de-sac, it was concluded that the process was secondary to adnexal torsion and infarction.[10]

Bicornuate uterus with a noncommunicating rudimentary uterine horn exemplifies the latter type of maldevelopment. The rudimentary horn is almost always lined by functional endometrium and is in continuity with a patent fallopian tube. The diagnosis is usually made during pregnancy,[11] most commonly when the pregnant noncommunicating rudimentary horn ruptures with catastrophic intraperitoneal hemorrhage.[12] It may lead to a missed abortion[13] or be discovered at the time of resection of a chronic abdominal pregnancy.[14] Recently it was found by serendipity at the time of cesarean section which led to the delivery of a live fetus.[15] A high index of suspicion resulted in resection of the pregnant noncommunicating uterine horn in three cases prior to rupture.[16] Although it is an unusual cause of dysmenorrhea, the correct preoperative diagnosis will be inferred when hysterosalpingography demonstrates a unicornuate uterus contralateral to a significant pelvic mass.[17]

Only five cases have been reported of bicornuate uterus with a noncommunicating, rudimentary, noncanalized, functionless uterine horn associated with ipsilateral partial fallopian tube atresia.[18] Two additional

From the Department of Obstetrics and Gynecology, Tufts University School of Medicine, Division of Reproductive Endocrinology, New England Medical Center Hospital.

Presented by invitation at the Forty-first Annual Meeting of the South Atlantic Association of Obstetricians and Gynecologists, Hot Springs, Virginia, January 28-31, 1979.

Reprint requests: Dr. Martin Farber, 171 Harrison Ave., Boston, Massachusetts 02111.

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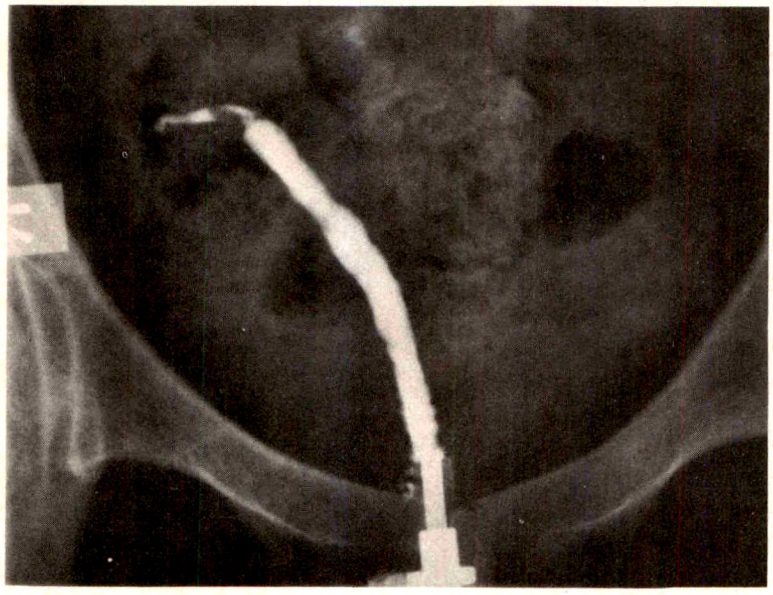


Fig. 1. Hysterosalpingogram demonstrating a right unicornuate uterus with an occluded tubal stump.

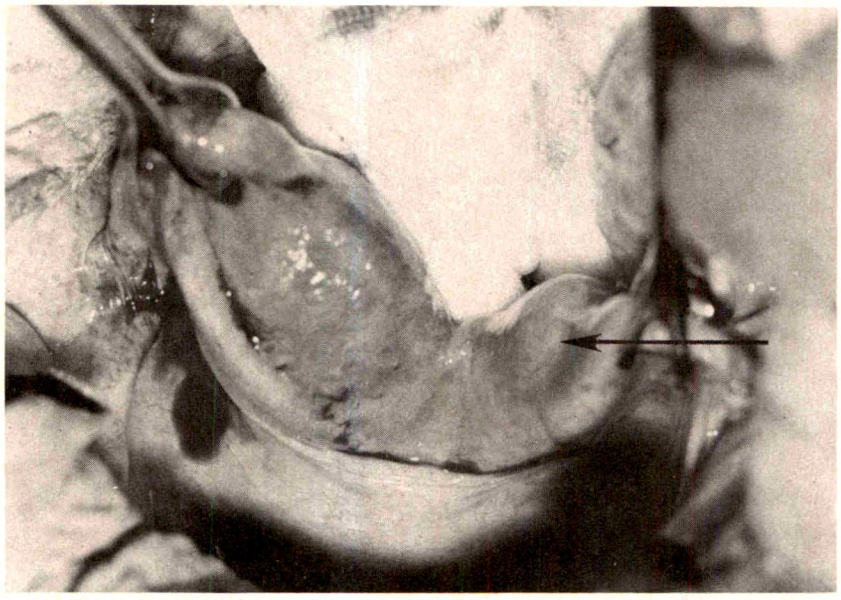


Fig. 2. Bicornuate uterus with a rudimentary left uterine horn (arrow).

cases are presented to effect an increased awareness of this anomaly and thus lead to intelligent clinical management.

Case reports

Case 1. A 23-year-old nulligravida woman who had undergone right salpingectomy and paraovarian cystectomy at age 18 was referred to the Division of Reproductive Endocrinology for primary infertility. At the time of initial laparotomy a bicornuate uterus was found with "bilaterally normally formed fallopian tubes." A hysterosalpingogram revealed a right unicornuate uterus with an occluded right tubal stump (Fig. 1). Hysteroscopy confirmed a lack of communication between the uterine horns. An intravenous pyelogram was normal.

Exploratory laparotomy revealed a bicornuate uterus but the left horn was rudimentary, measuring 3 cm in diameter (Fig. 2). It was situated in the folds of the left broad ligament, had no communication with the larger right horn, and was attached to the round ligament which exited through the internal inguinal ring.

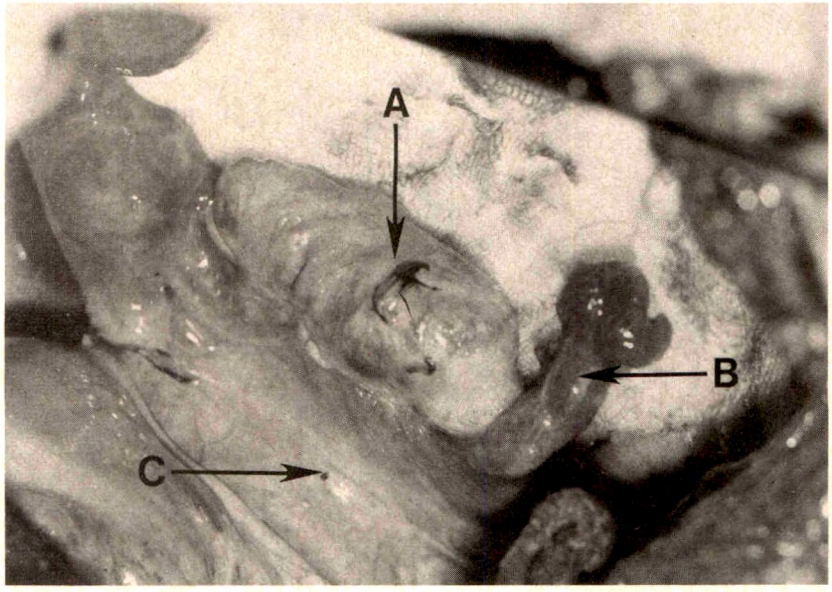


Fig. 3. The ovary *(A)* is interposed between the 1½ cm segment of left fallopian tube *(B)* which merges imperceptibly with the broad ligament *(C)* lateral to the rudimentary left uterine horn.

The right fallopian tube was absent. A 1½ cm canalized segment of left fallopian tube with a small, pale, fimbriated end was located 4 cm lateral to the rudimentary uterine horn (Fig. 3). Laterally it was contiguous with the left infundibulopelvic ligament and medially it merged imperceptibly with the broad ligament. The ovaries were grossly normal and there was no evidence of pelvic endometriosis. She was judged irreversibly sterile and the abdomen was closed.

Case 2. A 16-year-old nulligravid girl was referred to the Division of Reproductive Endocrinology for primary amenorrhea and cyclically recurrent pelvic pain of 3 months' duration. Secondary sexual characteristics were normal in chronologic and sequential appearance. Blood pressure was 140/90 mm Hg. Pelvic examination revealed the external genitalia to be normal. The vagina was 2 cm in depth and in the left posterior pelvis was a 10 cm fixed, firm, tender mass. An intravenous pyelogram demonstrated right renal hypogenesis; the vertical dimension of the right kidney was 6 cm and of the left kidney was 13.7 cm.

At laparotomy a bicornuate uterus with an atretic cervix was found (Fig. 4). The left horn was distended with blood and contiguous with a left hematosalpinx distally occluded by the left ovary. There was extensive pelvic endometriosis. The right uterine horn was rudimentary (2 cm in diameter), located in the leaves of the right broad ligament, and attached to the right round ligament which exited through the internal inguinal ring. A partially atretic fallopian tube canalized for 3 cm was located 4 cm lateral to the right horn. The left horn and ovary were excised and a neovagina was created utilizing Wharton's[19] technique.

Comment

The paired müllerian ducts arise as invaginations of coelomic epithelium opposite the third thoracic somite at the cephalic pole and lateral to the mesonephros. The ducts grow caudally in the mesenchyme and are intimately associated with the mesonephric ducts which they use as guides. At 8 weeks the paramesonephric ducts fuse at Müllers tubercle where they contact the posterior wall of the urogenital sinus (sinus tubercle). Fusion of the ducts proceeds in a craniad direction and dissolution of the resultant intervening septum to form a single genital canal is complete by 10½ weeks. The sinuvaginal bulbs, bilateral proliferations of cells at the region of the sinus tubercle, are augmented by a solid mass of cells of müllerian, mesonephric, or sinus origin that form the vaginal plate to completely occlude the vaginal tube. Ultimately the plate canalizes to form the vaginal lumen and by 21 weeks the entire genital canal has access to the exterior.[4]

A bicornuate uterus with a noncommunicating, nonfunctioning, rudimentary uterine horn associated with ipsilateral partial fallopian tube atresia represents very early failure in unilateral müllerian duct development and consequent failure of fusion. Because the rudimentary horn is functionless, in the absence of other associated anomalies to obstruct egress of the menstruum there is no pelvic pain and no abnormal mass. Although the potential exists for the nidation of an embryo in the partially atretic fallopian tube this has never been reported. The five reported cases were associated with normal vaginal development. There was

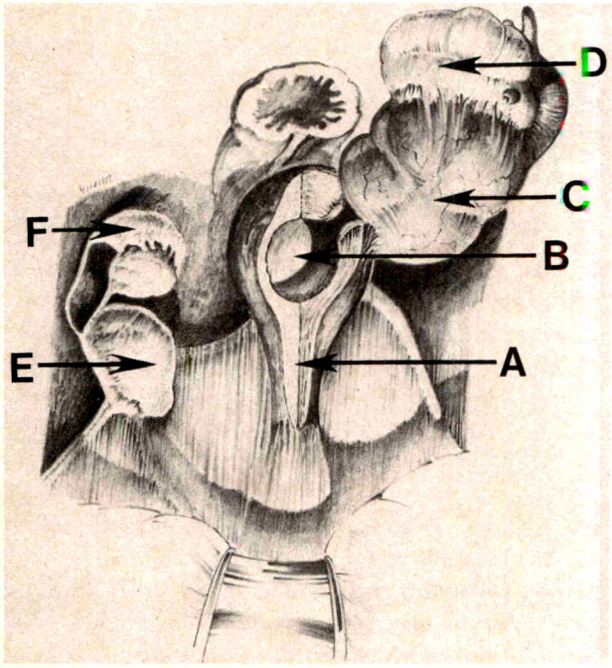


Fig. 4. The atretic cervix *(A)* has caused retrograde menstruation from the left uterine horn *(B)* to the resultant left hematosalpinx *(C)* distally occluded by the left ovary *(D)*. The right rudimentary uterine horn *(E)* is functionless and the right fallopian tube *(F)* only partially canalized.

no impairment of fertility and eight pregnancies were achieved in four patients. Two pregnancies terminated prematurely and four fetuses were small-for-dates.[17]

Knowledge of this anomaly suggests that extirpative adnexal surgery be performed with great caution in patients with double uteri and only after very careful assessment of the contralateral side. In our patients the short length of canalized fallopian tube precluded tubal implantation into the contralateral uterine horn, rendering the patients irreversibly sterile.

We are grateful for the technical assistance of Ms. Sarah Anderson in the preparation of this manuscript.

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Tubal ligation by colpotomy incision

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Columbus, Georgia

A five-year review of colpotomy tubal ligation performed on 585 patients within a private-practice setting in Columbus, Georgia, is analyzed. Operative time averaged under 30 minutes, and average hospital stay was less than 3 days. The major postoperative complication rate was less than 2%. The patient population is reviewed as to age, parity, previous contraception, and medical indications for sterilization. Surgical technique is discussed, and several suggestions are made. A follow-up of subsequent gynecologic procedures and the interval following colpotomy is then presented. (AM. J. OBSTET. GYNECOL. 134:885, 1979.)

A REVIEW OF 585 cases of bilateral partial salpingectomy via colpotomy incision is presented. These operative procedures were performed by a professional association of four private physicians over a 5 year span (from June, 1973, through June, 1978). All surgical procedures were performed at either the Columbus Medical Center or Doctors' Hospital in Columbus, Georgia.

The patient population is analyzed as to age, parity, and medical indications for sterilization. Surgical technique is briefly reviewed, and several suggestions are made. Hospital stay is discussed, and immediate and long-term complications are presented. A review of subsequent gynecologic procedures is then conducted with emphasis on surgical indications and the time interval from tubal ligation.

Material and methods

Patient population. The patients ranged in age from 16 to 46. Mean age of patients was 31 years (Table I). Parity ranged from 0 to 6, with a mean parity of 2 (Table II).

Seventy-eight patients or 13% of the total were pregnant and underwent concomitant therapeutic abortion by suction curettage at the time of colpotomy.

Indications. The great majority of patients presented for elective sterilization; however, 69 patients or 11.7% presented for sterilization for medical reasons (Table III).

Contraception prior to tubal ligation. Contraceptive methods practiced prior to the operative procedure reflect the balance seen in our practice (Table IV).

Surgical technique. No prophylactic antibiotics were employed. Shaving of the perineal area was avoided, and surgical preparation with Betadine scrub and solution was performed. The posterior cul-de-sac was entered by sharp dissection with LeHey thyroid tenacula utilized for cervical traction. Care was taken not to extend the colpotomy incision lateral to the medial edge of the uterosacral ligaments.

A right-angled Haney retractor was placed in the open cul-de-sac, and the fallopian tube was grasped with a Babcock clamp and identified up to the fimbria. The tube was then ligated in a Pomeroy fashion utilizing 1-0 plain suture material, with the tubal segments submitted for evaluation.

The posterior peritoneum was closed in a nonlocking fashion, and the same suture material was then continued in a locking fashion for closure of the vaginal cuff. Careful attention was given to the lateral extent of both the peritoneal and the cuff incisions to ensure total hemostasis. Curettage performed in all patients with the use of sharp curettage technique. Suction curettage was carried out in those patients requiring therapeutic abortion. Early ambulation was encouraged. Except in surgically complicated cases, patients were returned to normal activity at the time of hospital discharge. Restraint from sexual intercourse was advised until office follow-up 2 weeks after surgery.

Results

Hospital stay. Hospital stay ranged from 2 to 7 days. Average hospital stay was 2.5 days per patient (Table V).

Surgical operative time (from colpotomy incision to conclusion of curettage). Surgical operative time

Presented at the Forty-first Annual Meeting of the South Atlantic Association of Obstetricians and Gynecologists, Hot Springs, Virginia, January 28-31, 1979.

Reprint requests: Dr. Cecil F. Whitaker, Jr., 629 20th St., Columbus, Georgia 31904.

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Table I. Age of patients

Age	*No.*
<20	3
20-24	81
25-29	199
30-34	182
>35	120

Total patients: 585, mean age: 31.

Table II. Parity of patients

Parity	*No. of patients*
0	11
1	95
2	328
3	101
≥4	50

Total patients: 585.

Table III. Medical indications for sterilization

Indication	*No.*
Hypertension	21
Varicosities of vulva or lower extremities	12
Diabetes mellitus	9
Previous thrombophlebitis or pulmonary embolus	6
Renal disease	6
Genetic carrier disorders	3
Mental illness—neurosis or psychosis	3
Valvular heart disease	2
Rh sensitization	2
Mental retardation	2
Duodenal ulcer	2
Addison's disease	1
Total	69

Table IV. Contraception prior to procedure

Method	*No.*	*%*
Oral contraceptives	210	36
Mechanical	149	21
Intrauterine contraceptive device	125	26
None	31	5
Unknown	70	12
Total	585	100

Table V. Length of hospitalization

No. of days	*No. of patients*	
2	355	
3	186	
4	30	
5	90	2.4%
6	2	
7	3	

Average stay: 2.5 days.

Table VI. Surgical complications: Failed colpotomy approach requiring laparotomy

Reason	*No. of patients*
Chronic pelvic inflammatory disease	2
Operative hemorrhage	2*
Pelvic adhesions secondary to previous surgery	2
Endometriosis	1
Unexpected adnexal mass (dermoid)	1
	8†

*Estimated blood loss of 300 to 350 cc. No transfusion was required.
†1.37% of total.

Table VII. Surgical complications: Postoperative complications

Complication	*No. of patients*
Tuboovarian abscess	1
Cellulitis of vaginal cuff	2*
Postoperative hemorrhage	3†
Thrombophlebitis (deep)	1
Hepatitis secondary to halothane	1
Pneumonia	1
	9‡

*Both managed by antibiotics without incision and drainage.
†One required suture and two were controlled by packing.
‡1.53% of total.

ranged from 15 to 60 minutes with an average time of 25.7 minutes.

Surgical complications. Laparotomy was required for ligation of tubes in eight patients or 1.37%. The reasons are shown in Table VI.

Nine patients experienced postoperative complications which contributed to prolongation of hospital stay and morbidity. Vaginal cuff hematoma and cuff abscess requiring incision and drainage were noticeably absent (Table VII).

Subsequent gynecologic procedures. The overall incidence of subsequent gynecologic procedures was 7.9% (Table VIII). It is of interest to note that the incidence in patients over 30 years of age was 18.08%.

Comment

Tubal ligation through vaginal colpotomy incision has proved to be an effective and efficient method of sterilization. Hospital stay and operative time have proved acceptably short.

Attention to surgical hemostasis, concomitant curettage, and early ambulation are believed to contribute to our low instance of operative complications.

The follow-up time of this patient population is

Table VIII. Subsequent gynecologic procedures

Procedure	*No. of months after tubal ligation*	*Indication*	*No.*
Total vaginal hysterectomy	9-46 mo. (mean: 29 mo.)	Pelvic floor relaxation	8
		Persistent menorrhagia	4
		Pelvic pain/dysmenorrhea/adenomyosis	5
		Leiomyoma	3
		Carcinoma in situ	1
Total			21
Total abdominal hysterectomy	6-48 mo. (mean: 28 mo.)	Pelvic pain/dysmenorrhea/ adenomyosis-endometriosis	9
		Leiomyoma	4
		Adnexal pathology:	
		Chronic pelvic inflammatory disease	2
		Hemorrhagic corpus luteum cyst	1
		Ectopic pregnancy	1
		Dermoid cyst	1
Total			18
Curettage	6-40 mo. (mean: 20 mo.)	Menorrhagia	5
		Abnormal cytology	2
Total			7
Grand total			46

short, and sweeping conclusions cannot be drawn; however, the instance of subsequent gynecologic operative procedures and the indications for the same do not appear to be adversely affected by the preceding colpotomy ligation.

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Discussion

DR. STEPHEN G. ANDERSON, Winston-Salem, North Carolina (Official Guest). Dr. Whitaker has presented one of the larger series of vaginal tubal ligations to date. His results with tubal ligation by colpotomy incision compare very favorably with those previously reported. Average operating time of 25.7 minutes, average hospital stay of 2.5 days, failed colpotomy rate of 1.37%, and postoperative complication rate of 1.53% all rank in the lower range when compared with those of other studies. In a thorough review of female sterilization, Shepard[1] reported a mean complication rate of 3.7% in 3,706 interval vaginal tubal ligations with a range of 0% to 26.3%.[1]

There are two problems in placing Dr. Whitaker's report in proper perspective. First, the follow-up period is admittedly short, prohibiting consideration of long-term effects of vaginal tubal ligation such as the failure rate and possible effect on menstruation. Second, when these results are compared with those achieved by another method of sterilization, one risks comparing surgical proficiency rather than methods. I suspect that the excellent outcome in the present evaluation resulted from this series of vaginal tubal ligations being performed by experienced gynecologic surgeons who paid scrupulous attention to hemostasis and technique.

Since the incidence of female sterilization is increasing and the total number exceeds 670,000 yearly, consideration of sterilization methods is in order. At present, laparoscopic tubal cauterization with or without tubal division is by far the most common method of interval sterilization with more than 200,000 such procedures being performed yearly.[2] The logical question, it seems to me, is whether laparoscopy has more or less merit than vaginal tubal ligation as a method for interval sterilization.

The major complication rate of laparoscopic tubal cauterization has been reported by Hulka[2] as 0.37%. Kleppinger,[3] reviewing 4,361 laparoscopic procedures over a 5 year period, reported serious complications requiring laparotomy in only 0.47%, and my estimated average hospital stay of his patients was 1.8 days. More important, the complication rate decreased with expe-

rience of the staff, and serious bleeding and burn complications were eliminated entirely with the advent of the bipolar coagulating instrument.

Laparoscopic tubal cauterization will be favored over vaginal tubal ligation by most gynecologists for the following reasons. The results reported today are good, but those from laparoscopy are even better. The major complication rate of laparoscopic tubal cauterization is one third to one fifth that from vaginal tubal ligation. With laparoscopy, operating time and hospital stay are less; the procedure can be done on an outpatient basis and even with local anesthesia. Finally, the single-puncture technique allows female sterilization with little surgical assistance, thus increasing efficiency.

To consider the present report in more detail, I have the following questions:

1. Were there any failures resulting in pregnancy other than the one ectopic pregnancy reported?
2. Were physicians used routinely as surgical assistants? When I performed vaginal tubal ligations, "good help" often seemed the key to accomplishing the procedure easily.
3. Were any procedures done on an outpatient basis?
4. Did the patient with a tuboovarian abscess require hysterectomy?
5. Can you offer any personal comparison between vaginal and laparoscopic tubal ligation?

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DR. ROBERT T. HOOVER, Orlando, Florida. Surgical sterilization is becoming a commonly performed procedure. Dr. Whitaker has given us his experience with one of the accepted methods. The most commonly used methods include the minilaparotomy postpartum sterilization via the abdominal route, laparoscopic sterilization using coagulation, clips, or rings, and finally the vaginal approach.

In commenting on Dr. Whitaker's paper it seems that the following should be borne in mind. All methods must be compared and the technique indicated for the individual patient should be the one with the lowest morbidity. In discussing the vaginal approach and its attendant morbidity it must obviously be compared with the morbidity of minilaparotomy and laparoscopy. My experience with colpotomy from 1960 to 1971 is not great and a review of my charts revealed 178 colpotomies of all types. In 1972, following a short course in laparoscopy, I began to use the laparoscopic approach for sterilization and evaluation of the pelvis for abnormal changes. Since 1972, I have performed three colpotomies for sterilization, these being done at the patients' request. Of these 181 patients the average hospital stay was 2.6 days, ranging from 1 to 12 days. In this group of patients two major complications occurred, one being a bilateral tuboovarian abscess secondary to gram-negative organisms and the other a postsurgical hemorrhage brought on by premature intercourse. This required suturing following anesthesia. Dr. Whitaker reported on 585 patients who underwent colpotomy for sterilization purposes. This large group adds considerably to the literature and I think that his paper is timely. His technique is essentially the same as I have used with the exception of the added curettage. For those using colpotomy I would like to reinforce his special attention to the angle of the vaginal incision, as the vascularity in the area of the uterosacral ligament is extensive and most bleeding occurs at this point. I would like to ask Dr. Whitaker if the curettage in association with this procedure uncovered any abnormal changes that aided him in the care of his patients. He made no observation on this in his paper.

I noted that he performed the procedure on 11 nulliparous patients. As those of you who performed colpotomies are aware, this is not an easy task and I would like to congratulate him on his surgical ability. Of his 585 patients, 15.3% were pregnant at the time the colpotomy was done and had undergone a vacuum extraction for termination of the pregnancy. I would like to ask Dr. Whitaker if blood loss was increased in these patients and were any of them involved in the three episodes of excessive bleeding.

The hospital stay averaged 2 to 3 days and while this is quite short when compared with that for most abdominal operations I feel that it should be compared with that of its competing procedure, the laparoscopy, which is somewhat shorter, averaging approximately 1 day or even less.

In 193 of the surgical procedures a time of 30 minutes or greater was required to complete the procedure. This seems like an excessive amount of time, particularly when compared to that with laparoscopy, which in my hands varies from 12 to 20 minutes and none that I have done has required as much as 30 minutes. Of the surgical complications I feel that two deserve special attention: the tuboovarian abscess and the vaginal bleeding which required suturing. In all likelihood these are procedure related.

I find several disadvantages to the procedure as compared to the laparoscopic approach. First, the hospital stay is prolonged when compared with that of laparoscopy and in this day of increased awareness of medical cost this should be considered. Second, with respect to surgical time, the procedure takes 10 to 15 minutes longer than laparoscopy and this could increase morbidity.

In the process of discussing surgical sterilization with patients the vaginal approach should be offered as an alternative method to minilaparotomy and laparoscopy and if the patient so desires the alternative procedure should be done

Radical hysterectomy: A critical review of twenty-two years' experience

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One hundred seventy-eight patients who had radical hysterectomy performed for management of invasive carcinoma of the cervix over a 22 year period at the Medical University of South Carolina were critically analyzed. The degree of differentiation of the malignancy appeared to be of more significance than tumor size in Stage I lesions. With proper patient selection and excellent operative technique, survival rates well over 90% with minimal complications can be obtained. The radical hysterectomy should never be used in association with irradiation. (AM. J. OBSTET. GYNECOL. 134:889, 1979.)

THE IDEA of the surgical removal of a cancerous cervix can be accredited to J. Marion Sims in the early 1870s[1]; however, the surgical technique of the radical hysterectomy was developed by Wertheim[2] about 1900. X-irradiation and radium were discovered in the late 1890s, with their therapeutic use against cervical cancer being recognized about 1900.[3] Thus a debate began that continues to the present time as to the advantages and disadvantages of each of these two modalities in the management of cervical cancer.

Many retrospective studies have been published with varying results. Most deal with survival rates and complications. The purpose of this study is to analyze critically the radical hysterectomies performed at the Medical University of South Carolina by the Department of Obstetrics and Gynecology in an attempt to improve patient selection for radical hysterectomy in the future.

Methods

Since the opening of the Medical University Hospital in 1956, 2,838 women have been treated for carcinoma of the cervix. One hundred seventy-eight or 6% underwent radical hysterectomy. The patients within this 22 year span will be divided into two groups of 11 years each since a major change in management of cervical carcinoma occurred in July, 1967.

Prior to July, 1967 (Group 1—86 patients). Criteria for patient selection varied. The procedure was performed by several different surgeons and, at times, by an unassisted house officer. Preoperative irradiation was occasionally utilized.

After July, 1967 (Group 2—92 patients). Patient selection was standardized—individually selected, ideal candidates for operation with small lesions. All procedures were performed by a trained gynecologic oncologist. No preoperative irradiation was administered.

All inpatient and outpatient charts were reviewed by a single research technician with the data obtained placed on an IBM 370 computer for analysis. Specimens were re-evaluated by a single pathologist for cell type, histologic grade, and depth of invasion. All data was studied and analyzed by a biostatistician.

Results

When the socioeconomic status was grouped as private or indigent (Table I), a slightly higher percentage of the patients were indigent (51% to 45%). This difference was a reflection of Group 1. Seventy percent of the patients were white (Fig. 1) and no racial differ-

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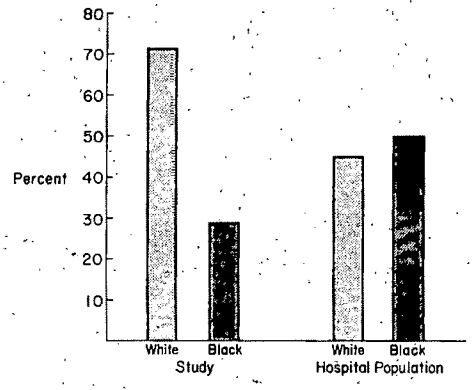


Fig. 1. Race of patients who had radical hysterectomy compared to that of hospital population (unknowns omitted).

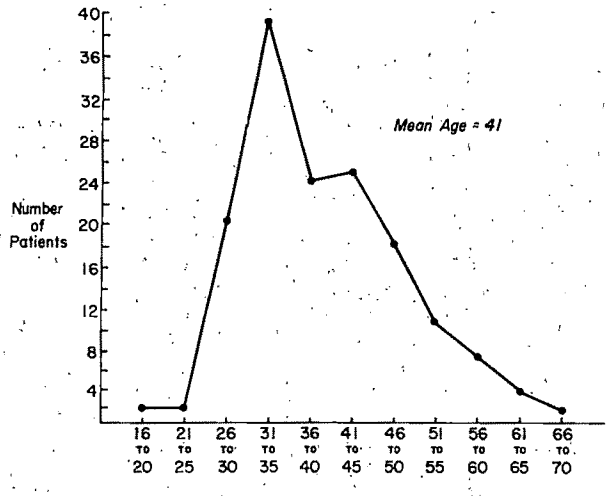


Fig. 2. Ages of patients, who had radical hysterectomy as grouped per 5 years (unknowns omitted).

ences existed between the two groups (P = 0.59). This markedly differed from the hospital population.

The clinical stage (International Federation of Gynecology and Obstetrics classification) is shown in Table II. The majority (62%) of the malignancies were Stage IB. No significant difference (P = 0.43) existed between the two groups. Seven patients had a cervical stump lesion.

The peak age for this procedure was between 31 and 35 years. The mean age was 41 years with ages varying from 16 to 70 years (Fig. 2). No differences existed between the two groups (P = 0.27). The 16-year-old patient had sarcoma botryoides.

The majority of patients weighed between 120 and 140 pounds (Fig. 3). Fifteen percent of Group 1 and 10% of Group 2 weighed over 150 pounds with 3% weighing over 200 pounds in both groups. The mean weight for the entire series was 155 pounds with

Table I. The socioeconomic status of patients who had radical hysterectomy

Status	Group 1	Group 2	Total
Private	35 (41%)	45 (49%)	80 (45%)
Indigent	46 (53%)	45 (49%)	91 (51%)
Unknown	5 (6%)	2 (2%)	7 (4%)
Total	86	92	178

Table II. The stage of disease in patients who had radical hysterectomy

Stage	Group 1	Group 2	Total
IA	20	33	53
IB	55	55	110
IIA	5	2	7
IIB	0	0	0
Recurrence	1	2	3
Unknown	5	0	5
Total	86	92	178

weights varying from 89 to 245 pounds. Group 1 had heavier women (P = 0.05).

Only 4% of the patients were nulliparous (Fig. 4) and almost half of the women had four or more children. Again no significant difference existed between the two groups (P = 0.28).

Sixty-three (35%) of the women were asymptomatic, and disease was suspected by an abnormal Papanicolaou smear (Table III). Postcoital spotting, the so-called presenting symptom of carcinoma of the cervix, was present in only 15%. Pain, the late symptom of cervical cancer, was the presenting symptom in 9%. The length of symptoms was significantly less in Group 2 (P = 0.03).

Factors that complicated the malignancy and/or surgical procedure are listed in Table IV. The patients with pelvic inflammatory disease and pyometra both did well without complications from the surgery; however, the patient with pyometra died of disease. The pregnant patients and those with cervical stump malignancy will be discussed later.

The status of all patients treated is illustrated in Table V. The corrected survival rate was calculated by omitting patients lost to follow-up and free of disease and patients who died of other causes. It should be pointed out that almost all patients who were lost to follow-up and free of disease or died of other causes did so after being observed 5 or more years. In the past 11 years, only one patient has been lost to follow-up

Table III. The presenting symptoms of the patients who had radical hysterectomy

Symptom	*No.*	*%*
None (abnormal Papanicolaou smear	63	35
Menorrhagia	31	18
Postcoital bleeding	26	15
Significant vaginal discharge	25	14
Pain	17	9
Other	3	2
Unknown	13	7
Total	178	100

Table IV. The presenting complications in the patients who had radical hysterectomy

Complication	*No.*
Pregnancy	10
Cervical stump	7
Fibroids (significant)	4
Pelvic inflammatory disease (active)	1
Pyometra	1

Table V. The status of patients treated by radical hysterectomy

	Group 1 (85 patients)*		*Group 2 (90 patients*)*	
Status	*5 yr.*	*10 yr.*	*3 yr.*	*5 yr.*
Living and free of disease	67	57	69	52
Died of disease	9	12	1	1
Died of other causes	3	5	0	0
Lost to follow-up and free of disease	6	11	1	1
Living with recurrence (radiated)	0	0	1	0
Total	85	85	72	54
Uncorrected survival rate	79%	68%	94%	96%
Corrected survival rate	89%	86%	99%	98%

Total 5 year survival rates: uncorrected, 86%; and corrected, 93%.

*One patient in Group 1 and two patients in Group 2 who had radical hysterectomy for recurrent carcinoma were omitted.

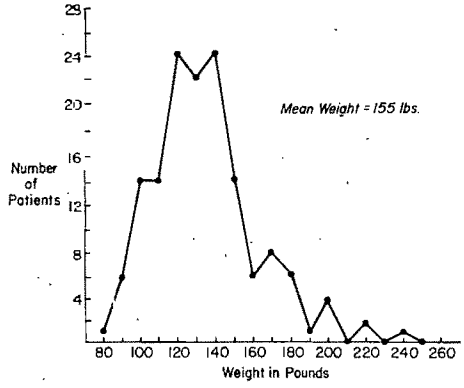


Fig. 3. Weight of patients who had radical hysterectomy as grouped per 10 pounds of body weight (unknowns omitted).

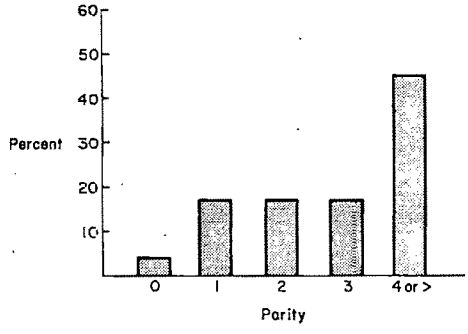


Fig. 4. Parity of patients who underwent radical hysterectomy (unknowns omitted).

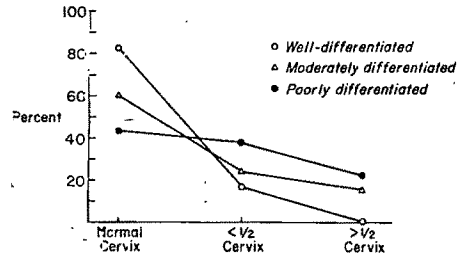


Fig. 5. Degree of differentiation compared to the amount of cervix clinically involved by neoplasm in patients who had radical hysterectomy.

prior to 5 years. She had microinvasive carcinoma and was lost to follow-up at 25 months. Therefore, the corrected survival rate should closely approximate true survival. A 5 year uncorrected survival rate of 86% and a corrected rate of 93% were calculated for the entire series. Only one cancer death occurred in the past 11 years; diagnosis, treatment, and death took place in 1977. Likewise the one patient with recurrence was treated less than 3 years ago, and the disease recurred in the vaginal apex. The patient received irradiation and is presently free of disease. Even though both of these patients were not eligible for calculation in 3 year survival rates, they were included for completeness. Six of the 10 patients who died at 5 years had poorly differentiated or undifferentiated malignancy. Three of the deaths occurred in patients with early Stage II lesions.

These patients were analyzed in an attempt to identify factors that could possibly have influenced survival and/or complications. Tumor volume was clinically estimated by two means—cervical size and the degree of

Table VI. Clinical estimate of cervical size in patients who had radical hysterectomy

Cervical size	*No. of patients*	*Living and well*	*Died of disease*	*Died of other causes*	*Lost, NED*	*Uncorrected survival rate (%)*	*Corrected survival rate (%)*
Normal	128	98	9	9	12	77	96
<6 cm	11	8	1	0	2	73	89
>6 cm	8	6	2	0	0	75	75
Unknown	31						
Total	178						

NED: No evidence of disease.

Table VII. Clinical estimate of degrees of cervical involvement by cancer in patients who had radical hysterectomy

Cervical involvement	*No. of patients*	*Living and well*	*Died of disease*	*Died of other causes*	*Lost, NED*	*Uncorrected survival rate (%)*	*Corrected survival rate (%)*
Normal	86	70	2	6	8	84	97
<Half of cervix	43	29	7	2	5	67	80
>Half of cervix	21	16	4	0	1	76	80
Unknown	28						
Total	178						

Table VIII. The clinical appearance of the cervix in patients who had radical hysterectomy

Cervix	*No. of patients*	*Living and well*	*Died of disease*	*Died of other causes*	*Lost, NED*	*Uncorrected survival rate (%)*	*Corrected survival rate (%)*
Normal	76	61	2	6	7	80	97
Granular	50	29	11	2	7	58	71
Ulcerative	20	20	0	0	0	100	100
Exophytic	4	1	2	1	0	25	33
Unknown	28						
Total	178						

Table IX. Cell type of malignancy in patients who underwent radical hysterectomy

Cell type	*No.*	*%*
Squamous carcinoma	133	75
Adenocarcinoma	23	13
Adenosquamous carcinoma	4	2
Sarcoma botryoides	1	1
Unknown	17	9
Total	178	100

Table X. The depth of stromal invasion in cervices with early disease from patients who had radical hysterectomy

Depth (mm)	*No.*
≤3	26
3.1-5	21
5.1-8	5

cervical involvement by tumor. In a retrospective manner, the clinical size of the cervix was estimated by interpretation of the original description of the cervix and grouped into three categories (Table VI). Group 1 had significantly more patients with larger cervices ($P = 0.004$). Although the numbers were small for statistical analysis, it appears that the larger the cervical size from cancer, the lower the survival rate.

By the other means of attempting to evaluate tumor volume, the cervical neoplasms were grouped as to the degree of cervix involved with cancer. (Table VII). Again Group 1 had more larger tumors ($P = 0.01$). These data suggest, but not statistically significantly, that once the cervix was clinically involved with neoplasm the prognosis did not change.

The clinical appearance of the cervix was grouped (Table VIII). A granular cervix rendered poor results and may reflect diffuse involvement. Of significance was 100% survival rate of the patients with ulcerative

Table XI. The degree of differentiation of the malignancy in patients who had radical hysterectomy

Degree of differentiation	*No. of patients*	*Living and well*	*Died of disease*	*Died of other causes*	*Lost, NED*	*Uncorrected survival rate (%)*	*Corrected survival rate (%)*
Well differentiated	17	15	0	0	2	88	100
Moderately differentiated	62	46	4	3	9	74	92
Poorly differentiated	41	28	8	4	1	68	78
Undifferentiated	3	1	2	0	0	33	33
Unknown	55						
Total	178						

Table XII. Pregnant patients who had radical hysterectomy

	No. of patients
Total patients	10 (6%)
Stage:	
IA	4
IB	5
IIA	1
Squamous cell type	
Trimester:	7
First	5
Second	2
Third	3
Blood loss (mean)	2,190 ml
Outcome:	
Free of disease	9 (54-206 mo.)
Died of disease (Stage IIA at 7 weeks' gestation)	1 (79 mo.)

Table XIII. Cervical stump lesions in patients who had radical hysterectomy

	No. of patients
Total patients	7 (4%)
Stage:	
IA	1
IB	6
Cell type:	
Squamous carcinoma	7
Adenocarcinoma	0
Outcome:	
Free of disease	6 (52-190 mo.)
Died of disease	1 (13 mo.)

Table XIV. Patients with positive pelvic nodes who had radical hysterectomy

	No. of patients
Total patients	8 (4%)
Stage:	
IA	0
IB	7
IIA	1
Cervical size:	
Normal	5
<6 cm	3
>6 cm	0
Cervical involvement (clinical estimate):	
Normal	2
<Half	3
>Half	3
Differentiation:	
Well differentiated	0
Moderately differentiated	1
Poorly differentiated or undifferentiated	6
Unknown	1
Outcome:	
Postoperative radiation	
Free of disease	3
Died of disease	1
No radiation	
Free of disease	0
Died of disease	3
Lost at 1 mo.	1

lesions as compared to the 33% survival rate of the patients with exophytic lesions.

Twenty-three (13%) of the patients had adenocarcinomas (Table IX). Nineteen were eligible for 5 year follow-up with a survival rate of 89%. Three patients died of disease at 12, 15, and 79 months, respectively. Two had Stage IB disease and one patient, at 7 weeks' gestation had Stage IIA disease. Only one patient had positive pelvic nodes. Of the four patients with adenosquamous carcinoma, one developed a vaginal recurrence at 3 months, and another was lost to follow-up at 1 month with positive nodes and was considered to have died of disease. This confirms the aggressiveness of adenosquamous carcinomas. The teenager with sarcoma botryoides of the cervix is living and well after 3 years.

The pathology slides that were considered adequate were measured for the exact depth of invasion. The early lesions (8 mm or less of invasion) are listed in Table X. No significant difference existed between the two groups ($P = 0.33$). No patient with 5 mm or less of invasion had positive nodes, developed a recurrence, or had a major complication. One patient in the 5.1 to 8 mm of invasion group is living with disease.

The degree of differentiation was determined in 123 patients (Table XI) and did not differ between the two groups ($P = 0.10$). None of the 17 patients with well-

Table XV. Preoperative irradiation in patients who had radical hysterectomy

	No. of patients	*Complication*	*Status*
Radium	7	2 Vesicovaginal fistula 3 Urethrovaginal fistula	5 Living and well 1 Died of cancer
External irradiation	1	None	Died of other causes
Radium and external irradiation	3	2 Urethrovaginal fistula 1 Colovaginal fistula	2 Died of disease 1 Died of complications
Unknown type	1	None	Living and well

Table XVI. Comparisons between the two groups who had radical hysterectomy

	Group			
	1	*2*	*Mean*	*Significance*
Blood loss (ml.)	2,176	1,102	1,603	T = 0.001
Days in hospital	20	13	16	T = 0.0001
Operative time (min.)	288	260	275	T = 0.09
Catheter (wk.)	3.4	3.4	3.4	T = 0.86

Table XVII. Operative injuries to urinary and gastrointestinal tracts in patients who had radical hysterectomy

	Groups	
Operative injury	*1*	*2*
Bladder	2	0
Ureteral	1	2
Rectal	1	0

Table XVIII. Fistulas in patients who had radical hysterectomy

	Group		
	1		
Fistula	*No.*	*%*	*2*
Vesicovaginal:		3	0
Nonirradiated	2		
Irradiated	1		
Ureterovaginal:		12	0
Nonirradiated	5		
Irradiated	5		
Colovaginal (irradiated)	1	1	0
	14	16	0
Nonirradiated fistula rate		8	0

differentiated malignancies died of disease. When the well-differentiated and moderately differentiated lesions were combined, the corrected survival rate was 94%. The number of recurrences drastically increased among the poorly differentiated and undifferentiated lesions. The combined corrected survival rate was 74%. When the degree of differentiation was compared to the clinical amount of cervix involved by tumor, a direct relationship existed (Fig. 5).

Ten patients were pregnant at the time of the diagnosis but none was less than 6 months post partum (Table XII). Of significance was that the mean blood loss was 2,190 ml (the mean for the series was 1,603 ml). The only death occurred in a patient with Stage IIA disease and she lived 79 months.

Seven patients had malignancy in the cervical stump (Table XIII). All were squamous malignancies and only one patient died of disease at 13 months.

Eight patients had positive pelvic nodes at radical hysterectomy (Table XIV). Of noteworthy significance were the following: (1) None had cervices over 6 cm; (2) only three lesions invaded over half way through the cervix; (3) six lesions were poorly differentiated or undifferentiated. Postoperative irradiation appeared to be beneficial since three of the four patients who received it were free of disease and three of the four who did not died.

In Group 1, 12 patients received preoperative irradiation (Table XV). Two thirds of these patients developed a fistula to the vagina and all patients who received both external irradiation and radium developed a fistula. These fistulas will be discussed in detail later. Six (50%) of these patients are living and free of disease. No preoperative irradiation was given in Group 2. Three patients had a modified radical hysterectomy for early central recurrence after primary irradiation. There were no postoperative complications; however, all died of disease. Two died in less than 1 year and one lived 37 months.

When the two groups were analyzed critically, significant differences existed in blood loss and days in hospital (Table XVI). Thirty-eight patients (41%) of Group 2 as compared to only 13 (17%) in Group 1 lost less than 1,000 ml of blood. On the opposite end of the scale, 12 patients in Group 1 and only one patient in Group 2 lost over 3,000 ml of blood.

Operative injuries to the urinary and gastrointestinal tracts are shown in Table XVII. All operative injuries were repaired primarily at surgery and healed without complications. Of interest was one patient in whom the ureter was transected at the common iliac artery at the beginning of the procedure. An end-to-end anastomosis was performed and healed primarily even

Table XIX. Correlation coefficients of several factors in patients who had radical hysterectomy*

	Time	*Blood loss*	*Postoperative complication*	*Intraoperative complication*	*Fistula*	*Days in hospital*	*Weight*
Time				0.008			
Blood loss	0.0001					0.004	0.004
Postoperative complication						0.003	
Intraoperative complication	0.007						
Fistula						0.0001	
Days in hospital	0.002	0.003	0.002		0.0001		
Weight		0.004					

*The numbers indicate the probability of a significant correlation. Only significant correlations are shown.

though the distal ureter was managed in the usual manner during the radical hysterectomy.

All postoperative fistulas occurred in Group 1 (Table XVIII). One of the three patients with vesicovaginal fistulas had preoperative radium. The other two were thin women with Stage IA and IB disease, respectively, who had no operative complication or other reason that could explain the fistula. Two fistulas closed spontaneously (including that in the patient who received preoperative radium) and the third patient refused surgery. She later developed a nonfunctioning right kidney and died 6 years later of other causes, free of disease, but with the fistula.

Ten patients developed ureterovaginal fistula. Five had received preoperative irradiation (three with radium only and two with x-irradiation and radium). There were no unusual characteristics in the five patients with no preoperative irradiation except three had prolonged procedures lasting over 5½ hours and three had a blood loss of over 2,500 ml. Fistulas in three of the nonirradiated patients, healed spontaneously; however, one patient later required a nephrectomy because of stone formation in the fistula site. Of the remaining two nonirradiated patients with fistulas, one required a nephrectomy and one an ileal conduit. All five are living and free of disease.

In the five patients who developed ureterovaginal fistulas and who received preoperative irradiation, one fistula closed spontaneously, two patients required nephrectomy, one an ileal conduit, and one received an unknown type of treatment. Two have died of the disease and three are living and free of disease. The patient with a colovaginal fistula died 3½ months postoperatively of infection.

Various factors were examined against one another for any significant correlation (Table XIX). Operative time was significantly related to blood loss, intraoperative complications, and days in the hospital. Weight was related only to blood loss.

The various factors studied were grouped within themselves and life tables for 5 year survival rates were calculated between Groups 1 and 2. Women who were under 35 years of age, weighed 110 to 134 pounds, had three or more children, and had operative procedures lasting less than 4 hours did significantly better in Group 2. None of the other factors showed any significant differences between the two groups.

Comment

The critical analysis of this series of radical hysterectomies reflects a departmental tendency to operate on the young, thin woman with a small Stage I neoplasm, especially in the past 11 years. The low incidence of only 4% positive pelvic nodes and the outstanding uncorrected survival rate of 86% and the corrected rate of 92% are undoubtedly directly related to this philosophy. The clinical estimate of the cervical size and degree of cervical involvement confirms this conservatism. The data confirm that the size of the cervical neoplasm is significant when related to survival; however, the degree of differentiation of the neoplasm appears to be of greater importance. There was a direct relationship between the degree of differentiation and the size of the cervical lesion.

Several important points can be obtained from these data: (1) Patients with well-differentiated and moderately differentiated tumors do far better than those with poorly differentiated and undifferentiated lesions. When the well-differentiated and moderately differentiated lesions are combined (79 patients) a corrected survival rate of 95% with only one patient with positive pelvic nodes indicates a too conservative approach in this series. (2) Two of the three patients with undifferentiated lesions died of disease despite their having small tumors. Also six of seven patients with positive nodes had poorly differentiated or undifferentiated carcinomas. (3) Three of seven patients with Stage IIA disease died of disease. (4) The patients with pure adenocarcinoma did well. (5) The adenosquamous carcinomas appear to act very aggressively. (6) Pregnancy did not affect the outcome.

Therefore, these data suggest that one could utilize

the radical hysterectomy as a means of management of a much larger Stage I carcinoma if it is well-differentiated or moderately differentiated. However, one should be very selective in performing radical hysterectomy in a patient with poorly differentiated or adenosquamous carcinoma and probably should never utilize it in the patient with undifferentiated carcinoma. These data also suggest that radical hysterectomy should not be performed in patients with Stage IIA or large, exophytic, Stage IB lesions and absolutely never in association with preoperative irradiation.

Surgical technique and experience in radical surgery cannot be overemphasized. This was reflected in blood loss, fistula formation, and days in the hospital over the past 11 years. Sharp rather than blunt dissection and ligation of the uterine artery and vein at their origin are two secrets to decreased blood loss. After ligation of the uterine artery and vein far laterally, they are lifted from over the ureter. This one procedure frees up over one half of the ureteral tunnels as well as the bloody part of the dissection. The identification of the ureter at its insertion in the bladder below the remaining tunnel renders the rest of the dissection easy and minimizes blood loss.

We believe that the most important points in preventing a ureteral-vaginal fistula are: (1) never directly handle the ureter and (2) preserve the blood supply to the ureter, especially at the lateral angle of its insertion into the bladder. The hypogastric and vesical arteries are left intact. Although the ureter is completely dissected from its bed in the broad ligament, the loose areolar tissue clinging to the ureter is carefully preserved. The ureter is sutured to the superior vesical artery to prevent it from dangling in the pelvis. As much peritoneum as technically possible is left attached to the ureter in the upper pelvis. Intravenous indigo carmine is injected after the removal of the specimen for identification of unsuspected lacerations.

Prophylactic antibiotic drugs and heparin, early mobilization, and extraperitoneal suction drainage minimize hospitalization. In the past 11 years, only one lymphocyst that required therapy has developed.

The radical hysterectomy has a definite role in the therapeutic armamentarium of the management of cervical carcinoma. Careful patient selection is the key to excellent outcome.

We wish to express our appreciation to Miss Wanda Fields and Mrs. Frances Mims for their assistance in the preparation of the manuscript.

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Discussion

DR. JOHN D. THOMPSON, Atlanta, Georgia. All the aspects of this fine paper that deserve discussion cannot possibly be included in the 5 minutes allotted to me, so I have chosen only a few points for discussion.

First of all, it should be made clear that this paper does not compare the results of irradiation therapy and surgical therapy for invasive cervical cancer. The authors would be the first to admit that many of the patients selected for primary radical surgery also would have been cured if irradiation had been chosen for primary therapy. In fact, if one does not select patients for primary surgery or primary irradiation therapy in Stage IB cervical cancer but assigns treatment to alternate patients in a manner perhaps similar to that of the fine study that was done by Dr. Michael Newton, one finds that the results of irradiation and the results of surgery are fairly similar, both in terms of cure and in terms of complications. It is sometimes forgotten that irradiation for cervical cancer is also associated with significant complications and also with a few late recurrences not often seen in patients treated with primary surgery. Radical surgery does, of course, have adverse effects on urinary tract function, but it should be remembered that irradiation therapy also has adverse effects on urinary tract functions.

The important point that the authors' paper demonstrates is that certain advantages of radical surgery over irradiation can be offered to selected patients with early invasive cervical cancer if the operation is performed by an experienced gynecologic surgeon who is familiar with the natural history of the disease, familiar with the technique of radical hysterectomy, and working in an environment in which the patient can be properly prepared for operation and properly cared for after operation. Primary surgery, for example, offers the distinct advantage of being able to determine by careful examination of the radical hysterectomy specimen the exact dimensions of involvement, especially as regards the extent of the central disease and the involvement of the pelvic lymph nodes in metastatic disease, and also gives additional insight into the de-

gree of dedifferentiation of the tumor and its propensity for invading lymphatic and vascular channels. This information is useful for forming opinions about prognosis and making decisions about the need of postoperative irradiation therapy. This information is not available when patients have a few random cervical biopsies taken and are then treated with irradiation therapy. All other things being equal, nothing prospers the correct management of the patient's problem more than knowing the full extent of disease.

But, in addition to a more accurate prognosis and a better plan of therapy, other advantages are evident for such selected patients. The largest number of the authors' patients were in the 31 to 35 year age group (39 patients) and 112 of 155 patients were age 45 years and younger. Adequate therapy for early invasive cervical cancer in such young women can be given with radical surgery without the necessity of removing the ovaries, thus preserving their useful function. The ovaries are rarely involved with metastatic disease from cervical cancer, even in late Stages III and IV. The ovaries will continue to function normally, and normal ovulatory cycles can occur, even after an extensive operation. Leaving the ovaries in place does not jeopardize the adequacy of the central dissection or the pelvic lymphadenectomy.

A recent Emory University study of sexual function following treatment for cervical cancer has shown us another clear advantage of primary surgery over primary irradiation therapy. Patients who received irradiation experienced statistically significant decreased sexual enjoyment, decreased ability to achieve orgasm, decreased libido, decreased frequency of intercourse, decreased opportunity for intercourse, and diminished sexual dreams. This is not surprising, since vaginal vault necrosis, pelvic fibrosis, irradiation cystitis and proctitis, and vaginal stenosis and dryness are frequent and loss of ovarian function is inevitable after irradiation therapy. The surgically treated group did not have any significant change in sexual function after treatment. This study was done by Drs. Machelle Seibel and Malcolm Freeman.

As one might expect, there are still variations in the technique of radical hysterectomy from one gynecologic surgeon to another. I believe the anterior trunk of the hypogastric artery and its distal branches, including the branches to the bladder, can be removed without increasing the incidence of ureteral-vaginal fistulas and with the advantage of allowing a more adequate central dissection. I have been reluctant to employ the minidose heparin schedule in patients with such an extensive pelvic dissection. Constant suction of retroperitoneal spaces for several days postoperatively until they are dry is an extremely important measure in reducing postoperative lymphocele formation and ureteral-vaginal fistulas. I do not believe it is necessary to suture the lower ureter to the superior vesical artery. In my experience, very thin patients are at greater risk of developing postoperative urinary fistulas following radical surgery. Perhaps this is because the operation has a tendency to be more complete when the patient is very thin. I fully agree that the results of radical hysterectomy can be quite satisfactory even though the operation is done during pregnancy. I also fully agree that preoperative irradiation has no place in a patient in whom radical hysterectomy is planned.

I would like to ask the following questions of Dr. Underwood:

1. What percent of patients with Stages IA, IB, and IIA disease were treated with radiation and what were the results of treatment?
2. What criteria are now used for the selection of irradiation or surgery as the primary therapy in these stages?
3. In this group of patients with predominantly favorable lesions, is it necessary or useful to remove a sample of the para-aortic nodes for frozen-section examination before proceeding with the radical hysterectomy?
4. Is one ever justified in not doing pelvic lymphadenectomy in patients with very early invasive cervical cancer, so long as the section around the central disease can still be adequate?
5. Is a pelvic lymphadenectomy to the bifurcation of the aorta always necessary?
6. Should patients who have a large cervical lesion (and perhaps because of this also an inadequate margin of resection around the central tumor), especially if the histologic grade is undifferentiated, in addition to patients found to have positive nodes, also receive postoperative pelvic irradiation?
7. Do patients in your series who undergo radical surgery and postoperative irradiation have difficulty tolerating this combined therapy?
8. Do you believe a patient with a large, Stage IB, undifferentiated cervical cancer will have a better chance of cure with fewer complications if treated with primary irradiation alone, primary radical surgery alone, or primary radical surgery followed by postoperative irradiation to the pelvis?
9. Finally, what are your views about conservation of normal ovaries at the time of radical hysterectomy and pelvic lymphadenectomy for invasive cervical cancer in young women?

At the Seventy-eighth Annual Meeting of the American Association of Obstetricians and Gynecologists in Hot Springs, Virginia (September, 1957), Dr. Clyde Randall discussed a paper on "Conservation of ovarian tissue in the treatment of carcinoma of the cervix with radical surgery." The paper was presented by Dr. Milton McCall.[1] In closing his discussion, Dr. Randall said, "It will be a strange line for the surgeon to claim superiority, not on the basis that danger can be totally excised, but rather on the basis of what can be preserved. We now find cervical carcinoma early and treat it so well that a majority of patients now survive more

than five years. Is it not time to consider modifying the treatment so that those we cure may live with bodies more nearly normal than many present day survivors possess?"

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DR. PHILLIP A. CARUSO, Fort Lauderdale, Florida. It has long been evident that radical hysterectomy can cure early invasive cancer of the cervix. Likewise, it is undeniable that irradiation therapy is nearly equally curative in such cases. There has been a dramatic improvement of both irradiation therapy and surgical technique within the past 20 years, resulting in a cure rate for Stage I carcinoma of the cervix in excess of 90%. This result has grown out of a mutual respect and healthy competitive spirit between therapeutic radiologists and gynecologic-oncologic surgeons. The problem of patient selection for each therapeutic modality remains a major issue for debate.

That both radical hysterectomy and irradiation therapy have survived as individually complete treatment for early invasive cancer of the cervix affirms that each has certain advantages over the other. While it is virtually impossible to determine if the 10% failures of each therapeutic modality would have benefited from the alternate form of therapy, it is only logical to look retrospectively at each group of such patients in the hopes of developing improved guidelines for optimum patient selection.

Dr. Underwood and his colleagues have reviewed 178 patients undergoing radical hysterectomy at the Medical University Hospital in Charleston, South Carolina, since its opening in 1956. They listed a multitude of adverse factors, including length of symptomatology, pyometra, loss of differentiation, advancing stage, size of the cervix, tumor volume, exophytic lesions, adenosquamous carcinoma, and increasing depth of penetration, not to mention the weight of the patient, prior irradiation, and inadequate surgical experience. On the contrary, pregnancy, adenocarcinoma of the cervix, and prior supracervical hysterectomy did not appear to adversely affect prognosis.

For these observations we must be grateful. I am not yet ready, however, to accept limited use of radical hysterectomy based upon a unilateral review of its shortcomings. When prospective studies indicate a definite benefit of irradiation therapy over radical hysterectomy in the management of poorly differentiated or adenosquamous carcinoma of the cervix, Stages IA and IB, I will reconsider this position.

Finally, I cannot help but entirely agree with the authors' views on surgical technique and their use of prophylactic antibiotics, minidose heparin, early mobilization, and extraperitoneal drainage. I sincerely compliment Dr. Underwood and his collaborators as their excellent results, especially within the past 11 years, bespeak the work of an experienced and talented surgical team.

I would like to ask Dr. Underwood the following questions. First, does he see any place for the use of combination irradiation and surgery as primary therapy in cancer of the cervix? Second, what tubing and suction apparatus has he found most to his liking?

Study of secretory component in patients with metastatic breast cancer

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A radicimmunoassay was developed for secretory component, a glandular epithelial cell product secreted as an accessory protein with dimeric immunoglobulins A and M. Forty-four normal women between the ages of 40 and 70 had plasma concentrations of secretory component of 7.195 μg/ml ± 3.590 (±2 SD). Of the 37 patients with metastatic breast cancer of epithelial origin, 34 (91.9%) had plasma concentrations greater than 8.990 μg/ml; 29 (78.1%) had plasma concentrations greater than 10.785 μg/ml; 10 (27%) had concentrations greater than 15.000 μg/ml; and 3 (8.1%) had concentrations greater than 22.710 μg/ml. Serial plasma concentrations (averaging 3.48 per patient) of 35 (94.6%) of these patients reflected the clinical course of the disease. All patients had some combination of surgery, radiation therapy, and chemotherapy. No direct correlation was noted between the type of therapy and concentration of secretory component. However, plasma secretory component served as a marker in the systemic circulation of a change in the status of the metastatic breast cancer. The impact of this research may lie in its incorporation into clinical management. (AM. J. OBSTET. GYNECOL. 134, 899, 1979.)

DESPITE INTENSIVE INTEREST, the goals of early diagnosis and subsequent monitoring of the progress of patients with breast carcinoma have not been achieved. The possibility of tumor markers for this dynamic disease has been suggested.[1, 2] Free secretory piece (FSP), an epithelial secretory protein, provides another potential opportunity to monitor the status of mammary carcinoma.

Recent laboratory investigation has shown an increase in FSP in several epithelial malignancies such as in the colon, lung, breast, bladder, and ovary.[3–5] After an increased plasma concentration of secretory component in patients with metastatic breast cancer of epithelial origin was hypothesized, the need arose for the development of a reproducible radioimmunoassay of high specificity and sensitivity for secretory component. The goal of this research was to develop a reproducible, specific, and sensitive radioimmunoassay for secretory component in the peripheral blood and relate the concentration to the clinical status of the patient.

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Presented by invitation at the Forty-first Annual Meeting of the South Atlantic Association of Obstetricians and Gynecologists, Hot Springs, Virginia, January 28-31, 1979.

Reprint requests: Dr. Stanley A. Gall, Box 3313, Duke University Medical Center, Durham, North Carolina 27710.

Material and methods

Purification of FSP. FSP was purified from human colostrum by the procedure of Kobayashi,[6] incorporating ammonium sulfate fractionation, ion exchange chromatography, and gel filtration. Protein fractions were followed spectrophotometrically at 280 nm and the method of Lowry and associates,[7] revealed the protein concentration of FSP to be 1.4 mg/ml. Contaminating lactoferrin was removed[8] and sodium dodecyl sulfate polyacrylamide gel electrophoresis revealed a singular band for the purified FSP.[9]

Production of antisera to FSP. Rabbits were injected subcutaneously with 1 mg FSP in complete Freunds' adjuvant weekly for 6 weeks. On the tenth week another dose was given. Eight days later, serum was drawn and absorbed with 120 mg lyophilized normal human plasma per milliliter serum. Immunodiffusion detected the anti-FSP activity and aliquots were stored

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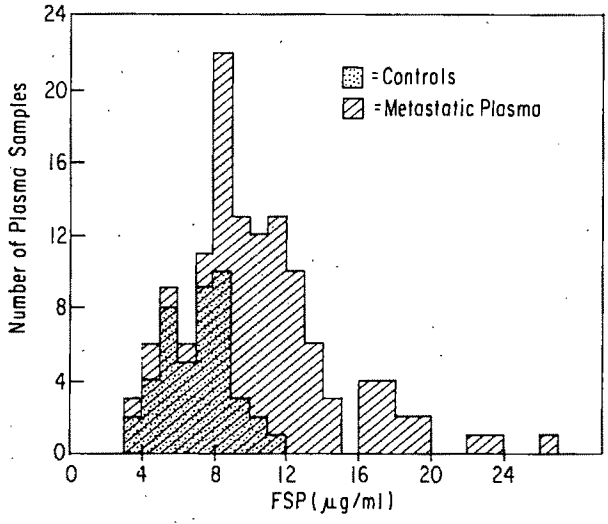


Fig. 1. FSP concentration and distribution in control patients and patients with metastatic disease.

at −20° C. When tested, this antiserum proved to be of the same potency as that obtained commercially.*

Labeling of FSP. The chloramine-T procedure was employed to label 98 mg (70 ml) of FSP with ^{125}I.[10] The labeled antigen was purified through a Sephadex G-50 column; the nonspecific protein fraction and the free ^{125}I fractions were discarded.

Determination of assay concentration of antiserum. Ammonium acetate, 0.1M, and albumin, 1 mg/ml, with sodium azide was employed to serially dilute the antibody in polypropylene tubes. Goat serum, 0.25 μl, was added to each dilution and incubated at 4° C overnight. Then 100 μl labeled antigen was added to each tube, incubated at 37° C for 4 hours, and total gamma emission/minute elicited. Precipitates were washed with Kynar† goat anti-rabbit–coated polymer beads. Kynar, 0.5 ml, was added to each tube, incubated at room temperature for half an hour, and mixed on a Vortex mixer every 10 minutes, and gamma emission/minute was again elicited. The percent bound to total counts was plotted, determining the assay concentration of antisera at 1/500.

Standard curve of precipitation. A two-stage inhibition curve for serial concentrations of cold FSP (0 to 50 ng) was prepared with each assay. Ammonium acetate, 0.1M, and albumin, 1 mg/ml, with sodium azide corrected the volumes to 500 μl. Antisera, 100 μl, was added to each tube and quenched with 25 μl goat serum. After incubation at 4° C overnight, 100 μl labeled antigen was added to each tube and gamma emission was noted. Optimal incubation proved to be 37° C for 4 hours. Precipitates were washed via the previously described Kynar procedure.

Samples. Serial plasma samples were obtained from 37 randomly selected patients with metastatic breast cancer from the Duke University Medical Center Department of Surgery. Plasma samples from 44 age-matched control subjects were obtained from the Columbia-Presbyterian Medical Center Department of Surgery. Samples were stored at −20° C and assayed in a double-blind manner. Clinical information was obtained directly from hospital records. All cancer patients had some combination of surgery, radiation therapy, and chemotherapy.

Assay procedure. Plasma samples, thawed at room temperature for 1 hour to avoid cryoprecipitate interference, were diluted 1/3,200. The sequential inhibition assay consisted of the addition of 100 μl of a 1/500 dilution of antisera with incubation at room temperature for 18 hours. Subsequently 100 μl labeled antigen was added with incubation at 37° C for 4 hours to reach equilibrium. The Kynar wash procedure was then employed.

The antigen proved to be stable and the reproducibility of the procedure was ±2%. Experimentation revealed that reduction and alkylation of the plasma samples as a pretreatment destroyed more antigenic sites than it freed. Alkylation alone had no effect on the data, suggesting that there was no consequential bonding of the label to nonspecific proteins or free immunoglobulins.

Results

Correlation of the plasma secretory component concentrations with the relative clinical information revealed the control range to be 7.195 μg/ml ± 3.590 (±2 SD) (Fig. 1). All samples tested with FSP concentrations greater than 11.185 μg/ml were from patients with a history of metastatic breast cancer. No correlation was noted between age, race, or type of therapy.

The patients with progressive metastatic breast cancer are a different population than the control subjects (Fig. 2), while FSP concentration is similar in control patients and in asymptomatic metastatic breast cancer patients (Fig. 3).

In some of the cancer patients, FSP concentrations were within the normal range despite active disease. Serial samples, however, reflected clinical improvement, stability, or progression.

Serial plasma FSP concentrations did not reflect the clinical status of two patients in this study.

Three illustrative cases are presented: the first with cancer progression, the second with positive response to chemotherapy, and the third with secretory compo-

*Behring Diagnostics, Somerville, New Jersey.

†Kynar, Hoffmann-La Roche Inc., Nutley, New Jersey.

nent concentrations monitoring the clinical course despite the absolute concentration being within the normal range.

Case reports

Patient A. This patient was treated with a radical mastectomy for medullary breast carcinoma and four of 22 lymph nodes were positive. Examination 10 months after operation was normal and FSP concentration was 10.880 μg/ml. The clinical condition remained stable and FSP concentration varied between 10.070 and 10.880 μg/ml. Seven months later, while she was hospitalized for evaluation of an axillary mass which proved to be a breast cancer metastasis, the FSP concentration was 19.200 μg/ml. Three weeks later she was discharged for terminal care by the family with a diagnosis of obstructive jaundice secondary to abdominal metastases. The FSP concentration at that time was 26.600 μg/ml.

Patient B. This patient, initially seen 2 years after radical mastectomy for papillary intraductal carcinoma with a positive liver scan, had a FSP concentration of 23.75 μg/ml. During the subsequent 3 weeks she had a beneficial response to chemotherapy and FSP concentration decreased to 17.930 μg/ml. A liver scan performed 2 weeks later revealed a decrease in metastatic lesions and FSP was 16.00 μg/ml.

Patient C. This patient underwent a radical mastectomy for mammary adenocarcinoma and six of 15 lymph nodes were positive. Initially she responded exceptionally well to chemotherapy and had a FSP concentration of 4.480 μg/ml. Within 3 months, however, metastatic pulmonary nodules appeared and FSP concentration had risen to 8.320 μg/ml. Chemotherapy was changed because of further progression. During the following 3 weeks her clinical status improved and FSP concentration decreased to 8.00 μg/ml. During the next 6 weeks she was asymptomatic with FSP concentrations of 5.600 and 5.300 μg/ml. However, the clinical condition deteriorated 5 months later and FSP concentration rose to 14.400 μg/ml. She subsequently developed abnormal liver chemistry tests and FSP concentration rose to 17.280 μg/ml.

Comment

Secretory component (molecular weight 70,000)[11] is believed to be a glandular epithelial cell product secreted as an accessory protein with dimeric immunoglobulins A (IGA) and (IGM) and containing a j chain. The immunoglobulins and j chain are synthesized by plasma cells.[11, 12]

Bound j chain is required for specific noncovalent bonding of secretory component to immunoglobulin.[13] The functions of secretory component are related to a homing mechanism for IgM polymers greater than 19S and for IgA, mediation of IgM and IgA travel through

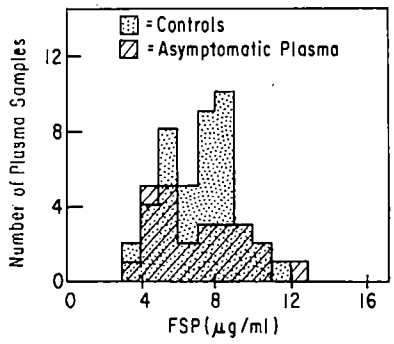


Fig. 2. FSP distribution in control patients and treated, asymptomatic cancer patients.

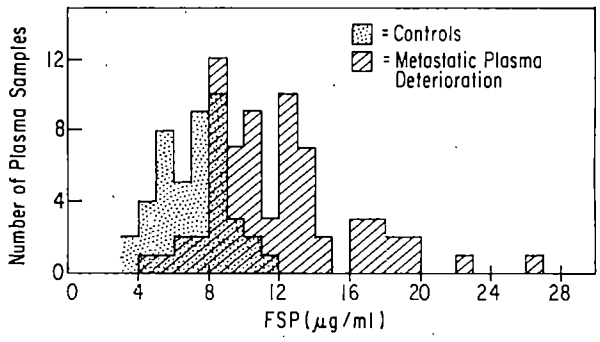


Fig. 3. FSP Distribution in control patients and cancer patients with progressive disease.

the epithelium to the lumen, and protection of the secreted immunoglobulin from proteolytic digestion.[14] Secretory IgA is the first line of defense against microbial invasion of mucous membranes.[11]

There are three antigenic sites on the secretory component molecule: A_1, A_2, and I. The I determinant is the most reactive but is inaccessible when secretory component is part of the IgA dimer. This determinant is the most readily inactivated by reduction and alkylation.[15]

The work of Garcia and associates[16] was a stimulus to our research in analysis of cystic effusions of ovarian epithelial neoplasms. Harris and colleagues[3] showed by direct immunofluorescence intense FSP antisera staining in stromal tumor cells. Normal breast cells revealed staining only in normal ductal epithelium. These investigators also demonstrated intense fluorescent staining in 50% of the patients with axillary node metastases. A lack of fluorescence was noted for patients with sarcomas of the breast.

One can therefore postulate that the increased secretory protein in tumor samples from patients with epithelial cancers reflects either increased production by malignant cells or absorption onto the malignant cells after synthesis in remaining normal ductal tissue. In either case, FSP is locally more abundant in mammary

malignancies of epithelial origin than in the normal breast.

The radioimmunoassay studies strongly suggest FSP was being measured because of identical curves obtained from purified FSP and comparable plasma samples.

Beyond detecting 34 (91.9%) of 37 cancer patients as having, at some time during the disease, plasma FSP concentrations greater than the normal range, this assay monitored the course of 35 (94.6%) of the 37 patients. No false positive results were noted.

The clinically significant potential of this assay may lie in screening and monitoring of therapeutic response and prognosis. In all likelihood, no one assay will provide all the relevant information, as human chorionic gonadotropin does for choriocarcinoma, but a group of complementary assays may certainly follow overlapping subsets of the population in question.[2]

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Discussion

DR. JOHN P. GUSDON, JR., Winston-Salem, North Carolina. The most significant advances that have been made in medicine are those which result in the eradication or significant decrease in the incidence of a disease. All of us have seen this happen in a number of diseases in which the etiologic agent has been identified. In a number of infectious diseases, immunization against that specific organism, or in the case of polio, those three organisms, has resulted in an almost total absence of the disease in the immunized populations. When the vector of a disease against which immunization is not feasible, such as yellow fever, has been identified and eradicated, the disease is "cured." In industry we have an example that is both pertinent to the topic of malignancy and current. The presence of high levels of asbestos in the atmosphere during the production of ships during World War II led to a significantly elevated incidence of bronchogenic carcinoma and mesothelioma in those shipyard workers. Stringent efforts, as a result of governmental regulations, to decrease the level of that agent in the atmosphere in shipyards have been effective in decreasing the incidence of those diseases. There are examples of preventive medicine at its best. This is the ultimate toward which we must strive.

However, for most diseases we are not yet there. Most of our time as physicians is spent in diagnosing and treating existing disease processes. Our limitations in the early diagnosis of a malignancy are known to all of us. Our frequently inadequate treatments are recognized and fully appreciated. Most physicians have felt the despair of seeing a malignancy progress. We must find a balance between the effects of our treatments, which are often very hard on our patients, and the disease process. For example, the addition of another chemotherapeutic agent such as adriamycin to the treatment regimen of a patient with Stage I carcinoma of the breast is certainly not warranted. It will probably do more harm than good. This, then, is the problem. What really is the true stage of the disease and is it progressing? These are the things we need to

know. This is the point at which the authors have developed an attack against carcinoma of the breast. This work is based on the discovery by Harris and colleagues (reference 3 of original paper) that the secretory piece of IgA existed in superabundance, as determined by histopathology, in various types of breast carcinomas. The authors questioned whether or not this would be reflected by an increase in the circulating secretory piece and whether or not the levels might reflect the clinical status of the patient.

They have, therefore, developed a radioimmunoassay for this substance and applied it to breast carcinoma patients. The relationship between the course of the disease and the level of circulating secretory piece is clear. The study was well founded and well done. I believe that we now have one more tool to use in our appraisal of the status of the disease in patients with carcinoma of the breast. I congratulate the authors of this paper.

Information for authors

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Maternal transport: Behind the drama

MICKI L. SOUMA, M.D.
Columbus, Georgia

Despite a lack of proof that overall perinatal outcome is improved, physicians and patients participate in a growing regional maternal transport program in a community hospital setting. Over the course of 3½ years, 129 patients were transferred from 23 institutions. Maternal transport and the changes which result in the interactions of the physicians are compared to traditional referral systems. Obstacles and guidelines for minimizing them are discussed. (AM. J. OBSTET. GYNECOL. 134:904, 1979.)

MATERNAL TRANSPORT is not new. Mothers have been brought for years from small hospitals to obstetric centers because of serious maternal problems necessitating personnel, equipment, and expertise beyond the capabilities of small institutions. The newer component of maternal transport is fetal transport, which involves moving mothers (who are usually relatively healthy) to a center in order to accomplish delivery in proximity to a nursery able to care for a potentially sick newborn infant.

The development of maternal transport for the latter purpose has followed a retraceable course: The value of neonatal intensive care units in reducing perinatal deaths was documented, and this advantage was extended to neonates born outside the institution of the specialized nursery through neonatal transport.[1-3] A logical assumption was made that the newborn infant would fare better if transported to the perinatal center in the atmosphere of the warmth, oxygen, and nutritive supply of the uterus rather than after delivery. National guidelines were developed for future coordination of such activities within an area.[4] Early reports have been promising. For example, local methods of maternal transport programs in Arizona and Colorado have been published and overall encouraging outcomes have been described.[5-7]

Transport activity traditionally brought drama to the small community, awed by the helicopter and the reports of the modern care miles away. It brought pride to the center and its personnel by recognition of their unique services.

However, the now increased activity of transferring a patient (soon to be two patients) from one institution to another has brought with it subtle changes in the interaction of physicians. These changes affect care and are worthy of attention since they are representative of changes occurring with regionalization of medical care in general. These changes make the overall success and growth of maternal transport the more impressive because of obstacles seemingly overcome.

The purpose of this paper is to present a unique community hospital–based maternal transport program as background for describing the observed changes in interaction of participants during the course of development of such a program. The observations are based on discussions with physicians, personnel, and patients.

Material and methods

The perinatal center at the Medical Center, Columbus, Georgia, has one of the five recognized newborn intensive care units of the state. The unit's early influence on the institution's perinatal mortality rate has been previously reported.[8] Newborn transport promptly followed the nursery's development. Prior to 1975, maternal transports were for traditional maternal indications and were arranged by calls directly to community physicians of choice or through the house staff (Family Practice Training Program). As fetal transport requests began in 1975, a program was developed to formalize the transport activities.

Maternal transports are received from a referral region of southwest Georgia and eastern Alabama. Receiving physicians are six obstetrician-gynecologists: two full-time hospital-based faculty in a Family Practice Training Program, two in private solo practice, and two in private group practice. Scheduling enables indi-

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vidual members of a group to participate without obligating all members. Calls for a transport are received in the Labor and Delivery Unit and are referred to the physician on call by use of a posted monthly roster. House staff participate actively in patient care but all transports must be personally authorized by the transport obstetrician-gynecologist. All patients are considered private patients regardless of the source of payment. The receiving physician first determines whether the transport pediatrician will be able to accept the potentially sick newborn infant. (Four pediatricians, one of whom is a neonatologist, are on call by a similar roster.) He then determines whether there are sufficient maternal beds to ensure adequate personnel coverage of all patients for whom the unit is responsible. Upon acceptance of a patient, the referring physician is asked to supply all records (including fetal monitor tracings and x-ray films) and provide a medical professional to accompany the patient (one-way transport). The patient is not considered the legal responsibility of the receiving institution and physician until admission at the door. Ambulance is the usual method of transfer but other methods range from helicopter (Military Assistance to Safety in Traffic of Fort Benning, Georgia) to family car.

At the receiving institution, family support is provided by personnel including maternal and newborn social workers. Financial status is reviewed for eligibility in state funding programs which by specific guidelines support optimum care of the high-risk patient.

An attempt is made to report to the referring physicians upon stabilization of the patient, delivery, change in newborn status, and dismissal. Discharge summaries are forwarded.

When a transport cannot be accepted, the transport physician assists the referring physician with alternative plans for maternal and newborn transport to another institution as needed.

Results

From June 1, 1975, through November 30, 1978 (42 months), 129 patients were accepted in transfer from 23 institutions. Communities sending patients in transport are listed in Table I. In the last 17 months of that time, transports "turned down" were documented as 20 for 58 accepted, or a ratio of approximately 1:3. Accepted transports increased over the 3½ years so that the number in the last 7 months of the program equalled that of the entire first year.

The reasons for transfer are listed in Table II, the majority being for the fetal indications of premature labor and premature ruptured membranes. The reasons for inability to accept the transport of 20 patients documented during the recent months of the program are indicated in Table III.

The reasons for no newborn beds included a full census, a shortage of beds because of remodeling, and closing of the unit because of an outbreak of bacterial infection. Maternal beds were also limited at times because of high census or remodeling.

On occasion patients who would need to be trans-

Table I. Communities referring maternal transport patients

Community	*No.*
Fort Benning, Georgia	72
Americus, Georgia	7
Thomasville, Georgia	6
Eufaula, Alabama	6
Albany, Georgia	6
Fort Rucker, Alabama	5
Moultrie, Georgia	5
Carrollton, Georgia	4
Richland, Georgia	2
Macon, Georgia	2
Lanett, Alabama	2
Cordele, Georgia	1
Woodbury, Georgia	1
West Point, Georgia	1
Fitzgerald, Georgia	1
Franklin, Georgia	1
Warner Robbins, Georgia	1
Arlington, Georgia	1
Dawson, Georgia	1
Columbus, Georgia	1
Sylvester, Georgia	1
Phenix City, Alabama	1
Fort Gaines, Georgia	1

Table II. Reasons for maternal transfer

Reason	*No.*
Premature:	
Premature labor	63
Premature ruptured membranes with or without premature labor	32
Pre-eclampsia, eclampsia	12
Third-trimester bleeding	7
Diabetes	4
Rh sensitization	2
Intrauterine death	1
Sickle cell crisis	1
Alcoholic coma	1
Total	123
Term:	
Rh sensitization	2
Diabetes	1
Obstructed labor	1
Intrauterine death	1
Previous cesarean section (transferred from hospital with no obstetrics unit)	1
Total	6

Table III. Reasons for turned-down maternal transfer

Reason	*No.*
No beds (for either mother or newborn infant) (assisted transport for mother or neonate as needed)	15
Funding for Alabama, not Georgia (assisted transport to Alabama center)	4
Gestation too immature (one subsequent neonatal transport)	2
Already delivered uncomplicated (hospital with no obstetrics unit)	1
Needed services available only at university program	1

Table IV. Outcome of 129 maternal transports

Outcome	*No.*
Undelivered (dismissed home or transferred back to referring institution)	28 (21.7%)
Delivered:	101 (78.3%)
Surviving infant	85 (4 sets of twins)
Neonatal death	17 (1 set of twins)
Fetal death (all prior to transport)	4

Table V. Outcome of 28 undelivered patients

Outcome	*No.*
Returned to Center for delivery:	11
Surviving neonate	9
Neonatal death	1
Fetal death	1
Delivered elsewhere:	15
Surviving neonate	16 (2 sets of twins)
Neonatal death	1
Fetal death	0
Neonatal transfer back	2
Still undelivered	2

ferred across the Georgia-Alabama state line were assisted in transfer to an Alabama center. Patients at less than 26 weeks' gestation were not accepted in the transport program for fetal indications only. An error in estimating gestation necessitated one subsequent neonatal transport. One patient with conjoined twins was referred to a University Center for management.

The outcome of the 129 pregnancies is presented in Table IV. Twenty-eight or 21.7% of the patients were dismissed for return to the referring institution or home. Of those 101 delivered, four fetal deaths occurred prior to transport. There were no posttransport fetal deaths. There were 17 neonatal deaths.

Most undelivered patients were dismissed as a result of successful control of premature labor. Others represented initial management for problems not yet warranting delivery. Of the 28 undelivered patients, eleven returned to the center for delivery and 15 were delivered elsewhere (Table V). The perinatal losses included one fetal and one neonatal death secondary to abruptio placentae. Both maternal patients had been hospitalized for several days during the earlier transport, for third-trimester bleeding. Of the 15 patients delivered elsewhere, two newborn infants required neonatal transport back to the center.

The overall perinatal mortality rate of the 127 delivered transported patients was 186.9 in comparison to 23.7 for the institution's total inborn population for the same time period. The perinatal mortality rate is defined as the sum of fetal and neonatal deaths occurring after 20 weeks' gestation or in infants weighing 500 grams or greater and newborn deaths occurring in the first 28 days of life per thousand live births.

Of the 102 live births occurring after the first transport, the predicted neonatal mortality risk using the classification published by Lubchenco and co-workers,[9] in 1972, is 24.7. The actual neonatal mortality rate was 16.7%.

The cesarean section rate of the transported patients was 33.0% for the 122 patients delivered at the Medical Center. The cesarean section rate for the institution's total deliveries during the same time period was 16.4%.

Comment

The activities of the transport program described here are similar to those previously reported in reasons for and methods of transfer.[6, 10] The percentage of undelivered patients (21.2) is remarkably similar to that reported by Brown[6] in describing the outcome of patients transported to Fitzsimons Army Medical Center (20.8). Interpretation of the overall perinatal mortality rate of this high-risk group of patients will be discussed following a commentary on the attitudes encountered in participants.

The referring physician. In the past the referring physician identified a problem beyond his institution's or his own capabilities. He then selected an institution and physician with those capabilities for transfer of his patient. His selection was based on geographic considerations, friendship, respect, prior handling of cases, his patient's own choice, and intangible aspects including fitting the personality of the patient to that of the physician. This usually necessitated a single phone call. The patient usually automatically transferred confidence to the new source of care by virtue of the need for the care and the selection process.

This has been changed. Attempts to refer by the old system may well be met with: "I would be happy to take your patient but we have a program now and Dr. X,

whom you do not know, in another group is on today" or "I would be happy to take your patient but the pediatrician will not accept the newborn infant because of commitments to eight other sick newborn infants" or "I would be happy to take your patient as I have done for the last 5 years but unless she is prepared to pay several thousand dollars we will be doing her a favor to assist in sending her to the center in your own state."

The one-to-one choosing of a physician by a patient or her personal physician is lost in the system. If the referring physician still had the prerogative to select, he might well choose a different institution for the baby than that preferred for the mother, the latter being influenced by private-practice competitiveness for his patient's future care (especially in short-distance urban transports) and by personal niceties available for the adult patient.

The referring physician is usually fully capable of delivering his or her patient. (Note that 74% of the referrals in our program were for indications of premature labor or premature ruptured membranes alone.) He may take pride in the ability to perform an even better delivery than could be done at the referral institution (certainly true if there is house staff participation in the care). Decisions regarding methods of care such as aggressive or conservative management of ruptured membranes are delegated to others with different approaches unless the impractical route is chosen of traveling to the site to make use of courtesy privileges. Even if all calls and records reach him, the physician has a disappointing loss of contact and personal experience with his patient.

When a decision is made to transfer despite all these obstacles, frustration is enhanced when the transport is turned down.

The receiving physician. In the old system, the receiving physician felt pride in being able to offer expertise and pride in his (or his institution's) being selected. Good-quality provision of care and detailed feedback strengthened ongoing referrals with the referring physician. In that atmosphere, the patient greeted him with confidence. Decisions to decline a case were a matter of personal conscience.

In the new system, the receiving physician is most frequently asked to accept a healthy patient in order subsequently to provide a sick patient to another physician. If the patient is not completely healthy, at times her obstetric problems (such as pre-eclampsia) have been managed for days by methods unlike his own, only to be referred at the point of decision for delivery with even the method of delivery selected. In a program in which it is the receiving pediatrician who authorizes the transport, the receiving obstetrician's sense of being only a technician, a necessary processor, is further heightened.

Table VI. Maternal transport sample telephone log

Accepted Maternal Transport
1. Notified of call by Labor and Delivery Unit. Checks on bed status of unit
2. Returns call to referring physician. Request for transfer placed
3. Calls Neonatal Intensive Care Unit to determine bed status
4. Calls pediatrician on call who authorizes use of last bed
5. Calls back referring physician, accepting patient and reviewing transfer of records and care
6. Notifies Emergency Room of anticipated ambulance arrival
7. Notifies Admitting Office
8. Notifies house staff and other participating personnel

Turned Down Maternal Transport
1. Notified of call by Labor and Delivery Unit
2. Calls Intensive Care Nursery to determine bed status
3. Calls pediatrician to request exception (exception not possible)
4. Returns call to referring physician, turning down transport and offering to assist transfer elsewhere
5. Calls second unit (repeat process, transfer accepted)
6. Notifies referring physician of acceptance, helicopter transport selected
7. Calls helicopter service (formal telephone application process)
8. Notifies referring hospital of estimated arrival time
9. Notifies receiving hospital of estimated arrival time

No referral can be handled by a single phone call. In fact, when it becomes necessary to turn down a transport, the receiving physician is often faced with as much time investment as required in accepting a patient (Table VI), work which often cannot be delegated to others, at least 24 hours a day. The turning down of a case in itself is difficult for physicians who in the old system correlated not taking a patient with laziness. The feeling of guilt is magnified when the outcome later reported for the turned-down case is perinatal death. On the other hand, patients who may have been declined in the past may be accepted for the sake of supporting an overall program (such as a patient in premature labor with a nonviable gestation).

"Transport back" brings a completely new experience in obstetrics as the "higher" center bears the responsibility for judgment in transfer. Errors in judgment occur, resulting in perinatal loss and exposing the human components of the system.

Finally, the receiving physician discovers a new responsibility for financial survival of the institution of the program. Local patients with uncomplicated pregnancies, who provide a major source of income, need their rightful priority. In a day when a source of payment for all bills must be identified, transports 100 miles across a state instead of 5 miles across a state line may be fairer to the patient.

The mother. Separated from her family, her own doctor, her locale, her expectations, she travels, often medicated, on a nightmare ride to be greeted by strangers and a bill she cannot pay, often with no baby to show for the anguish.

With all these obstacles, why do we continue, why is maternal transport an increasing activity?

The newborn infant. Does maternal transport offer an advantage to the newborn infant? Reliable data are lacking. Random comparison of maternal and newborn transports is affected by the automatic selection which occurs with newborn transport: exclusion of the very sick or very well after direct observation of the neonate. Merenstein and associates,[5] minimizing this influence by evaluating the entire population of two referring hospitals, showed a benefit of in utero transfer.

The Lubchenco neonatal risk scoring as used by Harris and colleagues[7] to compare maternal and newborn transports suggests an impressive advantage of maternal over newborn transport. His maternal transport neonatal loss was 60% of that predicted while neonatal transport loss was 1.26 times greater than predicted. Our program's maternal transport results compare favorably with those in the Arizona report, in that the neonatal mortality rate was 68% of that predicted. A comparison with newborn transport in our referral area during the same time period was not made.

This method, while reassuring that maternal transport does not negatively affect outcome, does not clarify the reason for the apparent advantage.

In our country's present system of care, maternal transport patients compared with newborn transport patients most often come from practices using more sophisticated methods. Even if maternal transports were evaluated within a single care system, they are preselected as those patients in whom delivery can be delayed long enough to allow travel. It may be the delay of delivery itself, not the transport, which provides the benefit.

The only meaningful study would be an impractical series prospectively alternating maternal transport versus newborn transport. Similar information may eventually be gleaned from comparison of accepted maternal transports with turned-down maternal transports which necessitate subsequent newborn transfer.

Despite the limitations in adequate evaluation of outcome, additional benefits of maternal transport cannot be denied. The mother remains with the baby, enabling development of maternal attachment.[11] Hunter and associates[12] showed victims of child abuse who survived neonatal intensive care had fewer visits by their parents in the nursery.[12] Furthermore, maternal transport is simply easier. Even if precautions must be taken for delivery en route, the investment in personnel time and cost cannot approach that of stabilization of a neonate during travel.[13–16]

These benefits seem a sufficient incentive for all participants to overcome the frustrations of a new system of care.

Suggested guidelines to improve interaction are as follows:

1. Community education about regionalized medical care so that transfer is not a shock to the patient and her family.

2. Educational program exchange between referring and receiving personnel to share management perspectives in order to merge the care of the patients into a single system.

3. Preagreed medical reasons for accepting or turning down a transport and preagreed nonmedical criteria for a closed unit and an alternate plan for patients seeking care.

4. Transfer of the patient's confidence from physician to physician and back again.

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Discussion

DR. JOHN S. INMAN, JR., Albany, Georgia. Optimum health care must be made available to all patients and to accomplish this goal the concept of regionalization has been developed. It is imperative that infants delivered of high-risk mothers immediately receive appropriate intensive care. To accomplish this goal it would be beneficial if the high-risk mother could be identified early in the course of her pregnancy and later transferred to a regional center where she could receive specialized care: her newborn baby could then be admitted to the high-risk intensive care nursery.

Dr. Souma has described the program of the Columbus, Georgia, Medical Center, one of the five Level III hospitals in the state of Georgia. Theoretically, a regionalization program should work smoothly because of our modern transportation system. Fortunately with the use of military helicopters and community ambulances all patients can be transported quickly to a Level III center.

There are many problems that must be overcome to make a regionalization system work. First, the attending physician must be convinced that his patient and her baby could receive better care at the Level III hospital. He should be very familiar with the program, so he could "sell" the patient on the idea of a transfer to another city. The attending physician should not have selfish motives and must be willing to transfer his private patient to the Level III physician. Second, the patient and her family must be "sold" on the idea of being transferred to a medical center some hundred miles from home. Many adjustments have to be made at home if the mother is to be away for several weeks.

In order to transfer a patient beds must be available for both mother and newborn baby. If beds are available then the transfer gets underway. If no beds are available the local physician has problems. Either he must try another Level III center or he must keep the patient and deliver the baby. This is hard for the family to understand and really puts the referring physician on the spot after he has convinced the patient and her family that she should be transferred. This can be a problem! Dr. Souma stated that in the last 17 months 20 referrals were declined and 58 accepted, approximately one patient declined for every three accepted.

To make a regionalization system work the community physician should know or at least know of the Level III physicians. A private physician–to–private physician relationship must be developed. Frequent communications by letter and by telephone are a necessity.

It takes time and much money to overcome many of the obstacles of a regionalization program. A similar program has worked well in the military services for many years. A military patient could be transferred from the small station hospital to the large general hospital with all its modern facilities and specialists with the greatest of ease. A similar program could be made to work for civilians. At no time, however, must the family physician feel that the obstetrician is trying to take his patients.

I am sure Dr. Souma would like to be able to accept more patients. Are there any plans for enlarging your facilities for both mother and baby? It seems to me declining one of four requests is rather high. This is indeed discouraging to the referring physicians.

Some physicians in our area do not understand the regionalization program and are reluctant to transfer their patients to another city. It would be helpful to have an educational program not only for physicians but also for patients. High-risk patients must be identified early in pregnancy and the staff of the regional centers must make themselves available for advice and consultation, not just for referral. I think it would be of great value if a physician and nurse could visit each medical community or hospital in southwest Georgia and explain the role of the tertiary care center. This would increase the number of referrals and in time decrease the perinatal mortality rate in our area.

As Dr. Souma has stated maternal transport with the fetus in utero is much better than newborn transport in reducing perinatal deaths. This makes it well worth the effort to create a system that satisfies both the referring and receiving physicians.

Dr. Souma, it is comforting to know that you are 85 miles away by highway or just 45 minutes by helicopter.

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DR. PRESTON LEA WILDS, Norfolk, Virginia. Dr. Souma has drawn a distinction between maternal transport for maternal indications and maternal transport for fetal indications. The emotional impact of this

distinction is important only to obstetricians. For the mother, the nightmare ride, the care by strangers, the separation from familiar surroundings, and the anxiety over the outcome are all the same. There are cases where transfer of the mother is advisable for both maternal and fetal indications, but in cases where early delivery of the fetus is the only special risk, the mother indeed may be the transport vehicle for the fetus.

The relative safety of fetal transport, with the mother as the vehicle, and neonatal transport, in which the vehicle is an appropriately equipped and staffed mobile intensive care unit, cannot be separated from the availability of specialized care to prevent perinatal asphyxia. Prevention of this asphyxia prior to birth is an obstetric responsibility. The quality of this care is seldom sufficient reason to justify fetal transport. The obstetrician working in a community hospital with limited resources can be as skilled in the detection and prevention of asphyxia in management of labor and delivery of the premature infant as the obstetrician in the medical center working with the assistance of a team of residents.

The critical difference between fetal and neonatal transport, which may affect perinatal outcome in the small premature infant, is skillful treatment during the first few minutes after birth. Asphyxia at this time greatly increases the likelihood of respiratory distress syndrome and intracranial hemorrhage. These and other complications in surviving infants can lead to prolonged crippling disorders such as bronchopulmonary dysplasia and impaired neurological development.

The immediate care of the infant born early in the third trimester requires special skills including manual dexterity and instant expert judgment, as well as all the proper equipment immediately available. The skills are easily lost unless they are practiced frequently. Most obstetricians and pediatricians, usually working with healthy, term infants, have inadequate opportunities to develop these skills and to maintain them at the necessary state of readiness. A medical center, where large numbers of premature infants are delivered and where a neonatologist is available to attend each delivery, can provide facilities in staffing to reduce the risks of neonatal asphyxia. It can also offer continuity of care to the premature infant and can often involve the mother as a participant in that care from the very beginning. These advantages are denied to the infant who is transferred to the medical center while the mother remains in a hospital elsewhere.

At the medical center in Norfolk, the nurseries connected with the labor and delivery unit have recently increased their intensive care capacity two and a half times. There has been no observable decrease in the pressure for beds, but there has been a shift in policy toward maternal transports. Requests for maternal transport are given priority over requests for neonatal transport and are usually accepted even when the nurseries are full or perhaps overloaded. Under these circumstances, acceptance of a maternal transport often requires a simultaneous reverse neonatal transport, in which a premature infant who is doing well is moved to an intermediate nursery elsewhere to make space available in the intensive care unit. The team of neonatologists has agreed to make these arrangements on an emergency basis in order to prevent denial of a maternal transport. As a consequence, in the past 3 months we have had to deny only one of 60 requested maternal transports because of lack of space.

A neonatologist attends each maternal transport delivery and is available on request for all other high-risk deliveries, including those where an attending pediatrician or chief pediatric resident is also present. These efforts on the part of the neonatologist to minimize perinatal asphyxia in all infants born at the medical center perhaps will lead to improved acceptance and understanding within the community of the benefits of maternal transport for fetal indications and, in time, may lead to further improvements in the outcome of pregnancy.

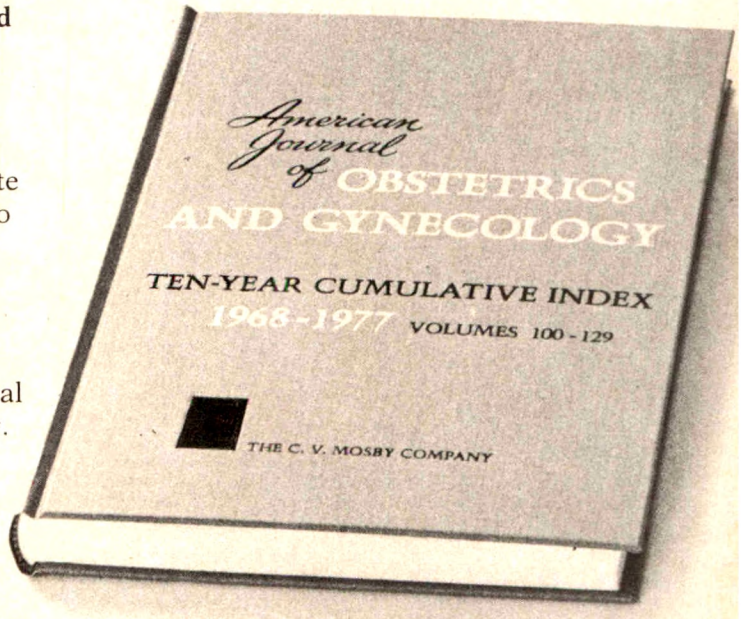
Dr. Souma has observed a continuing increase in the number of maternal transports, from relatively small beginnings, over a period of 42 months. I wonder, was there a point as the frequency of transports increased at which her perinatal team was getting sufficient practice in special skills to provide a stable level of optimum care for each small premature infant?

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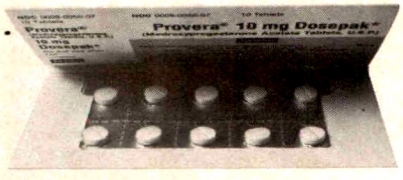
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Several reports suggest an association between intrauterine exposure to female sex hormones and congenital anomalies including congenital heart defects and limb reduction defects. One study estimated a 4.7-fold increased risk of limb reduction defects in infants exposed in utero to sex hormones (oral contraceptives, hormone withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some of these exposures were very short and involved only a few days of treatment. The data suggest that the risk of limb reduction defects in exposed fetuses is somewhat less than 1 in 1000.

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CONTRAINDICATIONS: Thrombophlebitis, thromboembolic disorders, cerebral apoplexy or patients with a past history of these conditions. Liver dysfunction or disease. Known or suspected malignancy of breast or genital organs. Undiagnosed vaginal bleeding. Missed abortion. Known sensitivity to medroxyprogesterone acetate. As a diagnostic test to pregnancy.

WARNINGS: 1. Immediately discontinue administration should any of the following thrombotic disorders occur or be suspected: thrombophlebitis, cerebrovascular disorders, pulmonary embolism, retinal thrombosis. **2.** Beagle dogs treated with medroxyprogesterone acetate developed mammary nodules, some of which were malignant. Although nodules occasionally appeared in control animals, they were intermittent in nature; whereas the nodules in the drug-treated animals were larger, more numerous, persistent, and there were some breast malignancies with metastases. Their significance with respect to humans has not been established. **3.** Discontinue medication pending examination if there is sudden partial or complete loss of vision, onset of proptosis, diplopia, or migraine. If papilledema or retinal vascular lesions occur, withdraw medication. **4.** Detectable amounts of progestin have been identified in the milk of mothers receiving the drug. The effect of this on the nursing infant has not been determined. **5.** Usage in pregnancy is not recommended (See Warning Box). **6.** Three major studies in Great Britain and one in this country have shown a statistically significant association between thrombophlebitis, pulmonary embolism, cerebral thrombosis and embolism, and the use of oral contraceptives. It has been estimated that users are several times as likely to undergo thromboembolic disease without evident cause as nonusers. The American study indicated that the risk did not persist after discontinuation and it was not enhanced by long continued administration.

PRECAUTIONS: A pretreatment physical exam should include special reference to breast and pelvic organs and a Papanicolaou smear. This drug may cause fluid retention, therefore, observe carefully patients with conditions influenced by fluid retention such as epilepsy, migraine, asthma, and cardiac or renal dysfunction. In irregular bleeding per vaginum, bear in mind nonfunctional causes and perform adequate diagnostic measures. Advise pathologist of therapy when submitting relevant specimens. Carefully observe patients with history of psychic depression and discontinue drug if serious depression recurs. Any possible influence of prolonged therapy on pituitary, ovarian, adrenal, hepatic, or uterine function awaits further study. Decreased glucose tolerance has been observed in a small percentage of patients on estrogen-progestin combinations, therefore, carefully observe diabetic patients receiving progestin therapy. Age constitutes no absolute limiting factor, although onset of climacteric may be masked. Because of the occasional occurrence of thrombotic disorders (thrombophlebitis, pulmonary embolism, retinal thrombosis, and cerebrovascular disorders) in patients taking estrogen-progestin combinations and since the mechanism is obscure, the physician should be alert to the earliest manifestation of these disorders. (See Patient Information for complete prescribing information.)

ADVERSE REACTIONS: Pregnancy: (See Warning Box); **Breast:** rare reports of breast tenderness or galactorrhea; **Skin:** sensitivity reactions including pruritus, urticaria, edema and generalized rash; acne, alopecia and hirsutism in a few patients; **Thromboembolic phenomena** including thrombophlebitis and pulmonary embolism.

The following adverse reactions have been observed in women taking progestins including medroxyprogesterone acetate: breakthrough bleeding; spotting; change in menstrual flow; amenorrhea; edema; change in weight; changes in cervical erosion and secretions; cholestatic jaundice; rash (allergic) with and without pruritus; and mental depression.

A statistically significant association has been demonstrated between use of estrogen-progestin combination drugs and the serious adverse reactions of thrombophlebitis, pulmonary embolism and cerebral thrombosis and embolism. Therefore, patients on progestin therapy should be carefully observed.

Although available evidence is suggestive, a relationship has been neither confirmed nor refuted for the association of the serious adverse reaction of neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis.

The following adverse reactions have been observed in patients receiving estrogen-progestin combination drugs: rise in blood pressure in susceptible individuals; premenstrual-like syndrome; changes in libido; changes in appetite; cystitis-like syndrome; headache; nervousness; dizziness; fatigue; backache; hirsutism; loss of scalp hair; erythema multiforme; erythema nodosum; hemorrhagic eruption; and itching. Therefore, observe patients on progestin therapy carefully.

The following laboratory results may be altered by the use of estrogen-progestin combination drugs: increased sulfobromophthalein retention and other hepatic function tests; coagulation tests (increase in prothrombin factors VII, VIII, IX and X); metyrapone test; pregnanediol determination; thyroid function tests (increase in PBI and butanol extractable protein bound-iodine, and decrease in T^3 uptake values).

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A report of the safety and accuracy of midtrimester amniocentesis at the Medical College of Georgia: Eight and one half years' experience

PAUL D. MANGANIELLO, M.D.
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Augusta, Georgia

HUMAN AMNIOTIC FLUID cells were successfully cultured and karyotyped in 1966.[1] The technique was used in the prenatal detection of chromosomal abnormalities starting in 1967.[2-4] The application of biochemical techniques to human amniotic fluid in 1968 extended the spectrum of detectable disorders to some inborn errors of metabolism.[4] In the following years, successful prenatal diagnosis was reported for a variety of isolated metabolic disorders.[5] Amniotic fluid alpha-fetoprotein (AFP) determinations for neural tube disorders (NTDs) in 1972 further expanded the indications for midtrimester amniocentesis.[6]

The success and increasing use of amniocentesis for prenatal diagnosis during this time span created the need to evaluate its safety and accuracy. In 1978, the findings of the collaborative study of the National Institute of Child Health and Human Development (NICHD) Amniotic Fluid Registry, created for this purpose, based upon 1,040 women who underwent diagnostic midtrimester amniocentesis, were published. The incidence of pregnancy loss was 3.5% in the amniocentesis group versus 3.2% in the control group. No clear evidence of direct fetal injury was reported from the nine participating centers. Maternal complications related to the procedure, such as transient bleeding and fluid loss, were reported to be 2%. Five incorrect cytogenetic diagnoses were discovered after delivery and one inborn error was incorrectly diagnosed. The overall accuracy rate of amniocentesis reported by these nine centers was 99.4%.[7]

Whether separate reports from different centers will confirm this collaborative study as to the safety and accuracy of prenatal diagnosis remains to be seen. This report is an 8½ year (June, 1969, to January, 1978) resumé of prenatal diagnosis at the Medical College of Georgia.

Material and methods

Patients were referred to the Medical College of Georgia for counseling and amniocentesis. The visit was scheduled between the fourteenth and eighteenth week of pregnancy, based upon the menstrual age provided by the referring physician. Preliminary ultrasonography has been routine since 1973. Maternal serum for AFP and Rh typing was obtained prior to the amniocentesis. The procedure has been performed utilizing a 20 gauge spinal needle by the attending physician or by a resident with the attending physician present. Supervision has been afforded by the same personnel since the inception of the study. The number of needle insertions per tap was not recorded in every instance. A minimum of 30 ml of amniotic fluid was removed and transported immediately to the adjoining laboratory for culturing. Fetal heart tones were documented and the patient was discharged. Rhogam was given routinely to unsensitized Rh-negative mothers. Subsequent patient and fetal follow-up was through correspondence directed to the referring physician.

Amniotic fluid cells were cultured in the Medical College of Georgia Cytogenetic Laboratory by standard techniques and stained routinely with Giemsa-trypsin

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Table I. Fetal deaths

Case No.	*Time interval from amniocentesis to documentation of death*	*Etiology of death*
1	Immediate	Cardiac needle*
2	7 days	Amnionitis†
3	7 days	Unknown*
4	28 days	Unknown*‡
5	36 days	Unknown*
6	36 days	Unknown*
7	Term stillbirth	Unknown
8	Term stillbirth	Postmaturity
9	Term stillbirth	Cord accident
10	Term stillbirth	Maternal hypertension
11	Neonatal	Rh sensitization*

*Tap related.

†Amnionitis present at time of amniocentesis.

‡Infant was found to have trisomy 21.

Table II. Indications for amniocentesis abnormalities detected

Indication	*Total pregnancies*	*Affected fetuses*
Chromosomal aberrations:		
Maternal age	149	3
Previous trisomy 21	33	1
Balanced translocation parent	8	3*
Remote history of trisomy 21	7	0
Total	197	7
Neural tube defect	30	0†
Sex-linked disorders	9	2 (male fetuses at risk)
Inborn errors of metabolism	3	2
Miscellaneous	13	0

*Four additional phenotypically normal fetuses had balanced translocations and are not included in this table.

†One closed neural tube abnormality was not detected prenatally.

banding. Supplementary banding techniques were used only as indicated. Following centrifugation, the amniotic fluid supernatant was sent by mail to the Eunice K. Shriver Center (1974 to 1977*) for determination of amniotic fluid AFP. Recently, maternal serum and amniotic fluid AFP determinations have been performed by Thomas Jefferson University.†

Results

The patient sample consisted of 252 patients who had diagnostic amniocentesis for genetic indications. Six pregnancies were lost to follow-up.

*Aubrey Milunsky, Ph.D., Eunice K. Shriver Center, Waltham, Massachusetts.

†Susan Cowchock, M.D., Thomas Jefferson University, Division of Medical Genetics, Philadelphia, Pennsylvania.

Procedural problems. The problems encountered with the procedure itself were (1) failure to obtain fluid and (2) failure, or delay, of cell cultivation.

Of the 252 patients referred for diagnostic amniocentesis, 233 (92%) required only one visit for a diagnosis to be made. Of the remaining 19 patients, no fluid could be obtained from one and 18 represented initial cultivation failures. Twelve of the initial 19 patients with diagnostic failures underwent a second amniocentesis. The remaining seven patients declined a second procedure. The second procedure was successful in 11 of the 12 remaining patients. One patient had an unsuccessful second amniocentesis. The latter individual plus the seven who declined a second procedure represent 8/252 (3%) of the study group who had no benefit from the procedure.

The mean time interval from fluid sampling to diagnosis was 17 days, ranging from 7 to 42 days. The time interval from fluid sampling to medically indicated termination of pregnancy was 4 to 5 weeks.

Maternal complications. Transient maternal complications, such as vaginal bleeding or amniotic fluid leakage, were not reported over the duration of the study.

Fetal loss. All spontaneous abortions, premature fetal deaths in utero, stillbirths at term, and neonatal deaths are considered together under the term "pregnancy or fetal loss."[7] The absence of fetal heart tones or motion on ultrasound prior to planned amniocentesis excluded a patient from the fetal loss category.

There were 11 fetal losses in the patient series. One of these was an immediate death secondary to fetal cardiac puncture. The remaining 10 fetal losses ranged from 7 days after amniocentesis up to and including the early neonatal period (Table I).

Five women experienced premature fetal death occurring 7 to 36 days after the amniocentesis. One of these fetuses, at the time of the initial diagnostic amniocentesis, had audible heart tones despite turbid, infected anmiotic fluid. A second premature postamniocentesis death at 28 days occurred in a fetus with trisomy 21. The other three had no apparent etiology except the amniocentesis.

There were four stillbirths at term. Two of these infants died during labor, of postmaturity and a cord accident, respectively. The third and fourth stillbirths at term were diagnosed when the mothers presented in labor. One of these was of unknown cause, while the other was related to maternal hypertension and diabetes. The tenth delayed fetal loss was caused by Rh sensitization. This patient had a positive indirect Coombs titer of 1:8 dilutions prior to amniocentesis. The amniotic fluid was free of blood, but maternal serum titers rose precipitately and intrauterine transfusion was re-

quired. The fetus died one week after birth as a result of Rh disease.

The overall number of fetal deaths encountered in this series was 11/252 (4.4%). Of these 11 fetal losses, only 6/252 (2.4%) were felt to bear some relationship to the tap (Cases 1, 3, 4, 5, 6, and 11, Table I).

Fetal morbidity. There was one case of mild hydrops fetalis, due to Rh isoimmunization, possibly related to the amniocentesis. The infant was born at term, treated with exchange transfusion, and did well in the neonatal period.

Indications and abnormal findings. Table II lists the primary indications for amniotic fluid studies and the abnormal findings in each group. The primary indication is defined as that indication for which the patient is at greater risk. For example, a 37-year-old female carrier of hemophilia is listed under "sex-linked disorders."

Chromosomal aberrations. There were 197 patients referred primarily for having a child at risk of a chromosomal aberration (78%). These patients can be subdivided into the following categories: maternal age-related nondisjunction, a previous trisomy 21 infant, a balanced translocation, and a remote family history of trisomy 21.

MATERNAL AGE. One hundred forty-nine patients were referred primarily at risk of maternal age-related nondisjunction. The majority of patients were seen between the ages of 35 and 44 (95%). In this group of patients, three abnormal amniotic fluid karyotypes were detected. Two mothers, both 37 years of age, had fetuses with trisomy 21; the third patient, age 41, was found to have a male infant with a 47,XXY karyotype (Klinefelter's syndrome). Both trisomy 21 pregnancies were interrupted and cytogenetic documentation was obtained from one by fetal skin karyotyping. The Klinefelter's syndrome pregnancy was not interrupted. Cytogenetic studies on the normal male newborn infant were confirmed as 47,XXY.

PREVIOUS TRISOMY 21 INFANT. Thirty-three couples, although cytogenetically normal, were referred with a history of having had one previous trisomy 21 infant. Amniotic fluid study revealed a repeat trisomy 21 in one of these couples. Pregnancy interruption with cytogenetic documentation was performed.

BALANCED TRANSLOCATION CARRIER. Amniotic fluid studies were performed on eight pregnancies in seven couples who were carriers of a balanced translocation in the peripheral blood. One amniotic fluid study was cytogenetically normal and four others revealed a balanced karyotype. Three studies were cytogenetically unbalanced. The first five pregnancies resulted in phenotypically normal children and the latter three had pregnancy interruptions. Two of the three unbalanced amniotic fluid studies represented consecutive pregnancies in the same patient. Cytogenetic confirmation of the antenatal diagnosis was obtained by peripheral blood studies in only one of these eight pregnancies.

REMOTE HISTORY OF TRISOMY 21. Seven couples presented because a remote relative had a child with clinical Down's syndrome. These couples usually presented in the second trimester and in most instances no accurate cytogenetic diagnosis was available on the affected relative. Amniotic fluid studies in these seven instances were normal.

NTDs. A total of 30 patients were referred because of NTDs. Twenty-seven patients had had one previously affected child, while three patients had two previously affected infants. One couple with one child affected with meningomyelocele also had a child affected with esophageal atresia. In this group there were no abnormal amniotic fluid karyotypes or elevated AFP levels. One false negative AFP value occurred in a patient who subsequently gave birth to a male infant with hydrocephaly, a closed neural tube disorder.

Sex-linked disorders. Nine patients were referred for sex-linked genetic disorders. Two patients at risk for hemophilia and Duchenne's dystrophy were diagnosed as carrying male fetuses. Both pregnancies were interrupted, but biochemical documentation of an affected male fetus was unsatisfactory in both instances.

Inborn errors of metabolism. Three patients were referred with a history of a relative affected with specific metabolic disorders. One patient had a history of two nephews affected with methylmalonic aciduria (MMA). Analysis of the amniotic fluid for MMA revealed an unaffected infant. Two other couples referred for metachromatic leukodystrophy and congenital adrenal hyperplasia were both found to have affected fetuses. The couple with the fetus affected with metachromatic leukodystrophy elected to undergo a therapeutic abortion. Histochemical documentation of metachromatic leukodystrophy was made in the aborted fetus. A male infant with confirmed congenital adrenal hyperplasia treated in the newborn period was born to the second couple.[8] There were no abnormal karyotypes or abnormal AFP values encountered in this group of patients.

Miscellaneous indications. Thirteen patients were classified as "miscellaneous." This group included couples with remote histories of abnormal undiagnosed family members. All parameters investigated (karyotype, AFP, and ultrasound) failed to disclose any abnormalities. No abnormalities were detected in the neonates.

Confirmation of diagnosis

Documentation of the amniotic fluid diagnosed was attempted whenever possible. All of the abnormal find-

ings were confirmed as correct by subsequent cytogenetic studies, fetal pathology, or enzymatic analysis.

One incorrect biochemical diagnosis was encountered. This occurred in a patient referred because of a previous infant with hydrocephaly. The AFP determinations were normal. The patient was delivered of a second child with hydrocephaly. Due to this "closed type" of NTD, the AFP values failed to reveal the abnormality.

During the study period, there were two amniotic fluid cytogenetic results which were not confirmed in the newborn infant. One amniotic fluid study revealed a dicentric number 20 chromosome in 33% of the cultured cells. The clinical significance of this cytogenetic abnormality was not known. The couple was advised that an accurate diagnosis of the child's phenotype could not be made. They elected to continue the pregnancy and a phenotypically normal infant was delivered. Peripheral blood cultures from the newborn infant failed to reveal this abnormality. The second case was an amniotic fluid mosaic 46,XX/46,XY. Among 30 cells counted, a single 46,XY cell was present in the amniotic fluid study. This XY cell line could not be detected in peripheral blood karyotyping of the normal term female infant.

Comment

The results of this smaller study, strictly supervised, do have some similarities to and differences from the collaborative NICHD study.

In the NICHD study, no diagnostic information was obtained in 27 patients (2.6%) because of tap or culture failure. The Medical College of Georgia (MCG) study subjected eight patients (3%) to amniocentesis without any tangible results. The absolute failure rate is very similar in both study groups and must be considered as one of the hazards of the procedure.

In the MCG group, only 19 patients, or 7.5% of the patient population, required a second procedure. This is considerably less than the 136 patients (13.1%) requiring a repeat tap in the NICHD study. Overall, in the smaller study group (MCG), there is a lesser incidence of diagnostic failures with the first amniocentesis. Second taps in the MCG study, when necessary, have been limited almost exclusively to initial culture failure. The principal reason for a second amniocentesis in the NICHD study was inability to obtain fluid at the initial tap.

In the collaborative study, 19 fetuses with chromosomal abnormalities (other than balanced translocations), 15 with metabolic disorders, and 11 male fetuses at risk of an X-linked disorder were detected in the total of 1,040 women, giving a 4.3% positive detection rate. In our series, 11 abnormalities (4.4%) were detected: three fetuses with trisomy 21, one fetus with Klinefelter's syndrome, three fetuses with unbalanced translocations, two male fetuses at risk of a sex-linked disorder, one fetus affected with metachromatic leukodystrophy, and one fetus affected with congenital adrenal hyperplasia. One closed neural tube abnormality was not detected prenatally and is not included in this figure.[11] Four balanced translocations similar to those in the collaborative study protocol are not included in the detection figure.

Misdiagnosis occurred in six instances in the collaborative study. Five of these were gross cytogenetic discrepancies between amniotic fluid and fetus. One was a positive amniotic fluid diagnosis of galactosemia in a normal infant. Only two cytogenetic misdiagnoses occurred in our series, both of them involving equivocal amniotic fluid findings that could not be identified in the two normal newborn infants. The closed neural tube defect and normal amniotic fluid AFP probably represented the limitations of the technique rather than misdiagnoses. The overall accuracy of the collaborative study was 99.4% compared to 98.8% in the MCG study.

In the collaborative study fetal death occurred in 3.5% of the total amniocentesis group. In this series there were 11 instances of fetal death (4.4%). Two of these cases, a fetal cardiac puncture and a postamniocentesis Rh sensitization with neonatal death, are clearly related to the tap. Four additional fetal deaths occurring in the postamniocentesis period had no discernible etiology. If the latter are assumed to be tap related, then six of the 11 pregnancy losses are causally related to the procedure. This gives a 2.4% overall tap-related mortality figure.

This series has a distressing number of term stillborn infants. The four stillbirths constitute 1.6% of the total amniocentesis group. In the collaborative series, the percentages of stillborn infants were 0.79% and 0.2% in the control and study groups, respectively. The increased number of term stillborn infants is puzzling. Although a causal relationship seems remote, one wonders whether the almost nonexistence of tap failures has been purchased at the cost of increased fetal deaths.

As each genetic center dating back to the late 1960s adds to the data pool, more information will be available to ensure the safety of prenatal diagnosis.

Harold Taylor, Ph.D., Roger Stevenson, M.D., Greenwood Genetics Center, Greenwood, South Carolina; Henry Nadler, M.D., Chicago Children's Memorial Hospital, Chicago, Illinois; and Chen Hung Ho, M.D., Genetics Division, Medical College of Georgia,

Augusta, Georgia, performed the determinations of aryl sulfatase A activity in cultivated amniotic fluid cells. W. Knowlton Hall, Ph.D., Gracewood State Hospital, Gracewood, Georgia performed the determinations of methylmalonic acid in amniotic fluid.

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Discussion

DR. FAY REDWINE, by invitation, Richmond, Virginia. This is the era of informed consent, and I think that the paper presented points out one of the most difficult questions about intrauterine genetic studies, that is, the question of risk. Risk of a midtrimester amniocentesis has been variously reported in the literature as not significantly different from that of a control group (reported by the NICHD National Registry for Amniocentesis Study Group) to a 1% to 3% incidence of direct fetal puncture (reported by Carp and Haddon in 1977) to a 13½% incidence of spontaneous rupture of the membranes within 5 days of the procedure (reported by Taramo and Sipinen in 1978). The problem with the literature is that most reports do not limit themselves strictly to amniocentesis for genetic studies but rather lump data from second- and third-trimester amniocentesis. One of the largest studies in the literature is by Galjaard (Cytogenetic cell genetics, 1976). He reported a series of 6,121 cases of prenatal diagnosis strictly for genetic disease, compiled from 46 centers in western Europe. The risk in that series of fetal loss following the amniocentesis was 1.4% with a range in different centers from 0.3% to 2.6%. As pointed out by the author, this falls within the range of spontaneous abortion during this period in pregnancy which was reported by the NICHD study as 3.2%.

This study, as are all studies in the literature except for the NICHD studies, is uncontrolled and due to this fact is somewhat difficult to analyze. The fetal mortality rate at the Medical College of Georgia was 4.4% which is higher than the control rate of the NICHD study but perhaps not higher than the fetal loss rate at that stage of gestation in Georgia. The corrected fetal mortality rate was 2.3%. I think that the conclusion of the NICHD study that the risk of amniocentesis for prenatal genetic studies is no greater than that of a control group may be statistically true, but one need only be presented with one case of an intracardiac fetal puncture and immediate death to know that amniocentesis must carry a risk of its own. In our series at the Medical College of Virginia, we have had one patient with chorioamnionitis developing 24 hours after amniocentesis, one with ruptured membranes the day of the procedure, and no other losses within two weeks of the procedure, giving a fetal mortality rate directly due to the amniocentesis of 0.5%.

Perhaps it seems quibbling to worry whether the complication rate is 0.5% or 4.4%, but in this study of 252 patients, seven patients were studied because of a remote family history of trisomy 21 and 13 patients were studied for miscellaneous indications. This is an incidence of 7.3% of amniocentesis done for a nonrecurrent genetic condition. Although in some cases anxiety alone may be adequate indication for intrauterine genetic studies, I do believe that determining an accurate complication rate is critical to adequately informing any patient but especially the ones with "miscellaneous nonindications."

The question of innate risk due to age is also an interesting one. In their total series of procedures done because of maternal age of 149 patients, two of the affected fetuses were in the maternal age group between 35 and 39 and one was in a patient over 40; however, the size of these subpopulations was not reported. From the series at the Medical College of Virginia, there has been an interesting trend. We have had four cases of nondysjunction in a group under 39 and one case in a 40-year-old patient. This is an incidence of risk for the 35 to 39 age group of 2.4% versus a risk in women 40 and older of 1% with both groups being composed of over 100 patients. We then find that the risk between 35 and 39 is actually greater than that over 40 in our series to date. It would be interesting if the authors from the Medical College of Georgia have looked at those statistics in that respect.

Perhaps one of the most exciting things about a series of this nature is what it does not include. The

future for the field of the intrauterine detection of genetically abnormal fetuses is very bright indeed. With the advent of gray-scale ultrasonography which enables us to measure fetal parts and examine fetal structure, real-time ultrasonography, which allows us to diagnose motion defects, such as cardiac abnormalities and urinary output, and fetoscopy, which has created for the first time the capability of obtaining fetal blood for diagnosis of hemoglobinopathies and muscular dystrophy, the scope of this field of interest is tremendous. I believe that groups such as the one at the Medical College of Georgia, combining the expertise of medical geneticists, obstetricians, and ultrasonographers, will enable us to use all of the modern advances in technology to allow our patients to reproduce safely.

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Hypothalamic-pituitary function and radiographic evaluation of women with hyperprolactinemia and an "empty" sella turcica

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A primary "empty" sella may be associated with significant hypothalamic-pituitary dysfunction. This report characterizes the endocrinologic and radiographic findings in six patients with hyperprolactinemia (range 34.3 to 1,170 ng/ml) ultimately found to have an enlarged empty sella. Lateral skull x-ray films and thin-section tomograms were suggestive of pituitary tumors in all patients. Four patients underwent transphenoidal sellar exploration after pneumoencephalography (PEG) failed to demonstrate air within the sella. The inability of PEG to demonstrate an empty sella in two patients was explainable on the basis of an intact diaphragma sellae with previous transient intrasellar pathology responsible for the sellar enlargement. Dynamic hypothalamic-pituitary testing yielded no consistent pattern of response. These studies suggest that an empty sella: (1) may be associated with hyperprolactinemia, regardless of etiology, (2) is not diagnosable by dynamic hormonal testing, and (3) may be indistinguishable from a pituitary tumor by current radiographic techniques. (AM. J. OBSTET. GYNECOL. 134:917, 1979.)

THE PRIMARY "EMPTY" SELLA syndrome is frequently diagnosed when air enters an enlarged empty sella turcica during pneumoencephalography (PEG) in a patient without previous sellar surgery or irradiation.[1] This syndrome may be associated with hypothalamic-pituitary dysfunction,[1–5] and the patients are characteristically obese, parous, middle-aged women with hypertension and headaches as frequent concomitant findings.[1]

The coexistence of a primary "empty" sella and galactorrhea with or without hyperprolactinemia has previously been reported[6–15] and, with two exceptions,[11, 15] prolactin (PRL) values have been reported as either normal or lower than those usually associated with functioning pituitary adenomas.[16] This report details our experience with six women complaining of amenorrhea or amenorrhea/galactorrhea who were ultimately diagnosed as having a primary "empty" sella and in whom hyperprolactinemia and the initial radiographic assessment strongly suggested pituitary tumor. In only two of the six patients described did PEG accurately diagnose an empty sella; the remaining cases were diagnosed at the time of transsphenoidal sellar exploration. The radiographic and hormonal assessment of these patients, as well as possible mechanisms of the hyperprolactinemia, is presented.

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Material and methods

A clinical profile of each of the patients is shown in Table I; Table II presents the initial baseline endocrine evaluation, and Table III illustrates the opthalmologic and radiographic assessment. Dynamic hypothalamic-pituitary axis testing was carried out utilizing: (1) the gonadotropin responses to luteinizing hormone–releasing hormone (LRF) stimulation (Figs. 1 and 2); (2) the growth hormone (GH) response to either insulin-induced hypoglycemia or arginine infusion (Fig. 3); and (3) L-dopa suppression of PRL (Fig. 4).

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Table I. Clinical profile

Case	*Weight (kg)*	*Height (cm)*	*Duration of galactorrhea*	*Duration of amenorrhea*	*Duration of hypertension*	*Headache*	*Visual disturbance*
1	77.3	164.5	2 mo.	Previous hysterectomy	None	"Frequent" and diffuse, 2 wk.	None
2	58.2	154.0	10 yr.	1 yr.	None	None	None
3	114.6	165.0	Unknown, not spontaneous	1 yr.	3 yr. (140/90 mm Hg)	"Mild," for 4 mo.	"Blurred vision" for several months
4	75.3	150	None	8 yr.	5 yr. (150/95 mm Hg)	"Frequent," for 15 yr.	None
5	130.0	173.0	7 yr.	7 yr.	8 yr. (130/100 mm Hg)	"Occasional," for 7 yr.	None
6	104.5	157.5	Unknown, not spontaneous	6 yr.	1 yr. (140/100 mm Hg)	"Mild," for 4 mo.	None

Table II. Baseline endocrine data (mean ± standard deviation)

Case	*Prolactin (ng/ml)*	*Estrogen (pg/ml)*	*T_4 (μg/100 ml)*	*TSH (μIU/ml)*	*Cortisol (μg/ml)*	
					PM	*AM*
Normal values	<20	*	5.0-13.7	<10	5-25	Twice value of PM cortisol
1	42.5	–	8.7	–	11	18.5
2	34.3	<20	8.3	3.0	9.7	3.8
3	125 135 143	100.5	7.1	–	5.8	21.4
4	43.6	–	5.2	4.5	9.9	8.6
5	1,170 930	<20	7.0	15	7.0	13.0
6	85 131.9 97.1	72.1	8.0	4.6	–	12.2

*Normal values (mean ± 2 SD): follicular phase, 82 ± 58; midcycle, 290 ± 115; luteal phase, 128 ± 103.

Table III. Ophthalmologic and radiographic assessment

Case	*Visual fields*	*Lateral skull x-ray film*	*Thin-section tomograms*	*PEG*
1	Normal	Symmetrically enlarged sella	Empty sella, no soft tissue apparent	Air entered an enlarged sella
2	Normal	Abnormal sella consistent with an expanding intrasellar lesion	Thinning and ballooning of anterior sella with dorsum completely eroded	Air entered an enlarged sella
3	Normal	Symmetrically enlarged sella	Asymmetrically enlarged sella without erosion	No air in sella, no suprasellar extension of tumor
4	Complete blindness of right eye, normal left visual field	Mild enlargement of sella	Enlarged sella with some erosion of floor	Failed twice because of an incompetent cisterna magna and failure to fill ventricles
5	Normal	Suspicious for tumor	Suspicious for tumor	No air in sella, no suprasellar extension of tumor
6	Normal	Double floor of sella	Definite tumor with focal ballooning	No air in sella, no suprasellar extension of tumor

Medications when first evaluated
Conjugated equine estrogens, 0.625 mg orally every day; diazepam, 5 mg orally every day
None
Chlorthalidone, 100 mg every day; oxtriphylline, 100 mg orally 4 times a day; terbutaline sulfate, 5 mg orally 3 times a day
Diazepam, 1 mg orally 3 times a day
Ortho-Novum-2, (norethindrone, 2 mg, and mestranol, 0.10 mg), in a cyclic fashion; thiothixene, 2 mg orally 3 times a day; Rauzide, 1 tablet orally twice a day powdered rauwolfia serpentina, 50 mg and bendroflumethiazide, 4 mg)
Diazepam, 5 mg orally every day; Chlorthalidone, 50 mg orally every day

Serum values for total estrogen (E), luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactin (PRL), growth hormone (GH), and thyroid-stimulating hormone (TSH) were obtained by standard clinical radioimmunoassay. Serum values for thyroxine (T_4) and cortisol were obtained by competitive protein-binding analysis. Normal values for these hormones at this institution are included in Table II. Responses to dynamic pituitary tests considered normal were: (1) a rise of GH to a value of 6 ng/ml or greater in response to either an insulin-induced 50% reduction in blood sugar (0.1 U insulin/kg administered intravenously) or an intravenous infusion of a 10% arginine solution (0.5 gm/kg); (2) a decrease of PRL of 50% or greater in response to a single oral dose of L-dopa (10 mg/kg); and (3) a "normal" response to LRF. While there is no well-accepted normal pattern of gonadotropin response to a single 100 μg subcutaneous injection of synthetic LRF (AY-24031, courtesy of Ayerst Labs.), the range of values from 18 normally cycling women tested in the early follicular phase of the cycle was used for comparison. The Second International Reference Preparation of human menopausal gonadotropin was used for the gonadotropin assays.

Case reports

Case 1. The first patient, a 43-year-old, black woman, para 6-0-0-6, presented with "fullness" in both breasts for "several" years with bilateral galactorrhea, greater on the left, noted for 2 months prior to admission. Menses were regular until 6 months previously when she underwent removal of the uterus, tubes, and ovaries for enlarging uterine leiomyomas and was placed on a regimen of Premarin, 1.25 mg orally, 25 days per month. The diagnosis of an empty sella was made when air entered the sella during PEG (Fig. 5) and no further diagnostic or therapeutic measures were recommended. Galactorrhea has continued to the present time.

Case 2. The second patient, a 27-year-old, black woman, para 2-0-0-2, presented with a 10 year history of galactorrhea coincident with oral contraceptive use and a 1 year history of amenorrhea after discontinuance. She underwent laparoscopic tubal cauterization in March, 1977, and discontinued oral contraceptives with no further menses. The diagnosis of a primary "empty" sella was made when air entered the sella during PEG (Fig. 5). Galactorrhea and amenorrhea have persisted to the present time.

Case 3. The third patient, a 38-year-old, massively obese, black woman, para 5-0-0-5, had cyclic menses from her last delivery in 1971 until April, 1975, when she developed amenorrhea. She denied galactorrhea, but Sudan IV–positive fluid was easily expressible from both breasts on examination. The diagnosis of a pituitary microadenoma was advanced but at transsphenoidal exploration the patient was found to have an arachnoid diverticulum filling the sella. Biopsies revealed only normal pituitary tissue. No return of menstrual function has occurred and galactorrhea persists.

Case 4. The fourth patient, an obese, 36-year-old, white woman, para 0-0-0-0, was referred with an 8 year history of amenorrhea without galactorrhea. Menses had been irregular since menarche at age 12, after 2 years of amenorrhea she was noted to have an enlarged sella on a lateral skull x-ray film at age 30. She had congenital blindness of the right eye secondary to a coloboma and was found to have polycystic kidneys in 1972. Two attempts at PEG were unsuccessful because of incompetence of the cisterna magna and inability to fill the vertricular system or the suprasellar cistern. Because of partial anterior hypopituitarism and the likelihood of a pituitary adenoma, she underwent transsphenoidal exploration of the sella. A large arachnoid diverticulum was found to nearly fill the sella with the pituitary compressed posteriorly. The diaphragma sellae was incomplete, allowing visualization of a portion of the optic chiasm. Microbiopsy of the pituitary remnant revealed only fibrovascular tissue (compatible with an atrophic anterior pituitary). The hypopituitarism has persisted postoperatively and the patient requires vasopressin nasal spray to control mild diabetes insipidus.

Case 5. This patient, a 39-year-old, massively obese, black woman, para 2-0-0-2, presented with 7 years of amenorrhea/galactorrhea. Her last delivery had occurred 10 years prior to admission, and she had used oral contraceptives for 2 years post partum, with resumption of cyclic menses upon their discontinuance, 2 years prior to the onset of amenorrhea/galactorrhea. Because of the massive elevation of PRL a pituitary

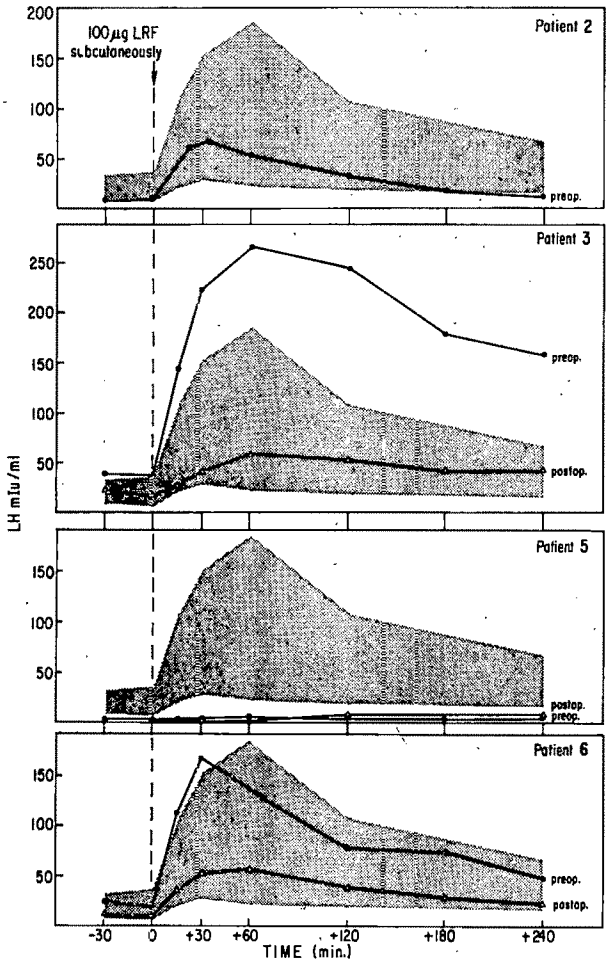


Fig. 1. LH response to a single subcutaneous injection of 100 μg of LRF. The shaded area represents the range of normal values in 18 cycling women tested in the early follicular phase of the menstrual cycle. No consistent pattern of LH response was observed, with Case 3 above, Case 5 below, and Cases 2 and 6 within the normal range.

tumor was thought to be present but at surgery the patient was found to have a large, empty sella with multiple arachnoid trabeculations and adhesions within the sella. The pituitary was noted to be atrophic and displaced posteriorly to the left; no tumor could be identified at surgery. Serum PRL level determined immediately *prior* to surgery, but not available the day of surgery, revealed a marked drop (1,170 to 64 ng/ml). It has remained at this level during the 2 years since surgery and the patient remains galactorrheic with a single episode of vaginal spotting several months postoperatively.

Case 6. The sixth patient, a 38-year-old, obese, white woman, para 0-0-0-0, had cyclic menses until 1969, when she began having irregular menses, bleeding approximately every 3 months, and after another year she developed amenorrhea. She denied galactorrhea but had easily expressible Sudan IV–positive galactorrhea on examination. Because of hyperprolactinemia

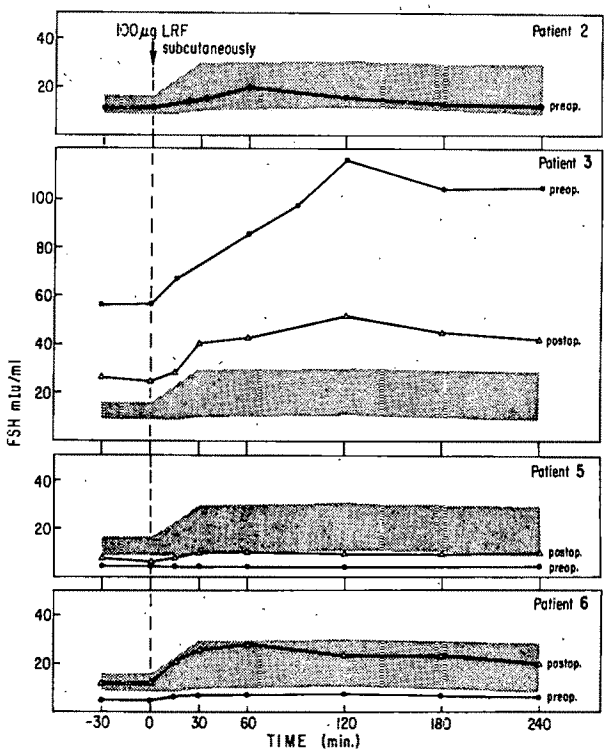


Fig. 2. FSH response to a single subcutaneous injection of 100 μg of LRF. The shaded area represents the range of normal in 18 cycling women tested in the early follicular phase of the menstrual cycle. There was no consistent FSH response, with Case 3 above, and Cases 2 and 5 below, and Case 6 within the normal range.

and obvious sellar erosion on polytomography, she underwent transsphenoidal exploration but at surgery the sellar abnormality, though lined with dura, contained only strands of nondescript fibrous tissue. Microbiopsy of the pituitary gland revealed no evidence of tumor. Serum PRL returned to the normal range postoperatively, the galactorrhea ceased, and cyclic menses have resumed.

Comment

Speculation as to the etiology of the primary "empty" sella focuses upon four theories. In the first, a congenitally absent or incompetent diaphragma sellae allows herniation of an arachnoid diverticulum with resultant transmission of cerebrospinal fluid (CSF) pressure, compressing the pituitary and enlarging the sella. In support of this theory, Busch[17] and Kaufman and Chamberlin[18] found absence of the diaphragma sellae frequently at routine postmortem examination. Second, transient physiologic or pathologic hyperplasia of the pituitary enlarges the sella, resulting in an empty sella when the gland returns to normal size.[19] Multiple pregnancies and treated primary hypothyroidism, respectively, represent such physiologic and pathologic entities. Third, because of the precarious blood supply

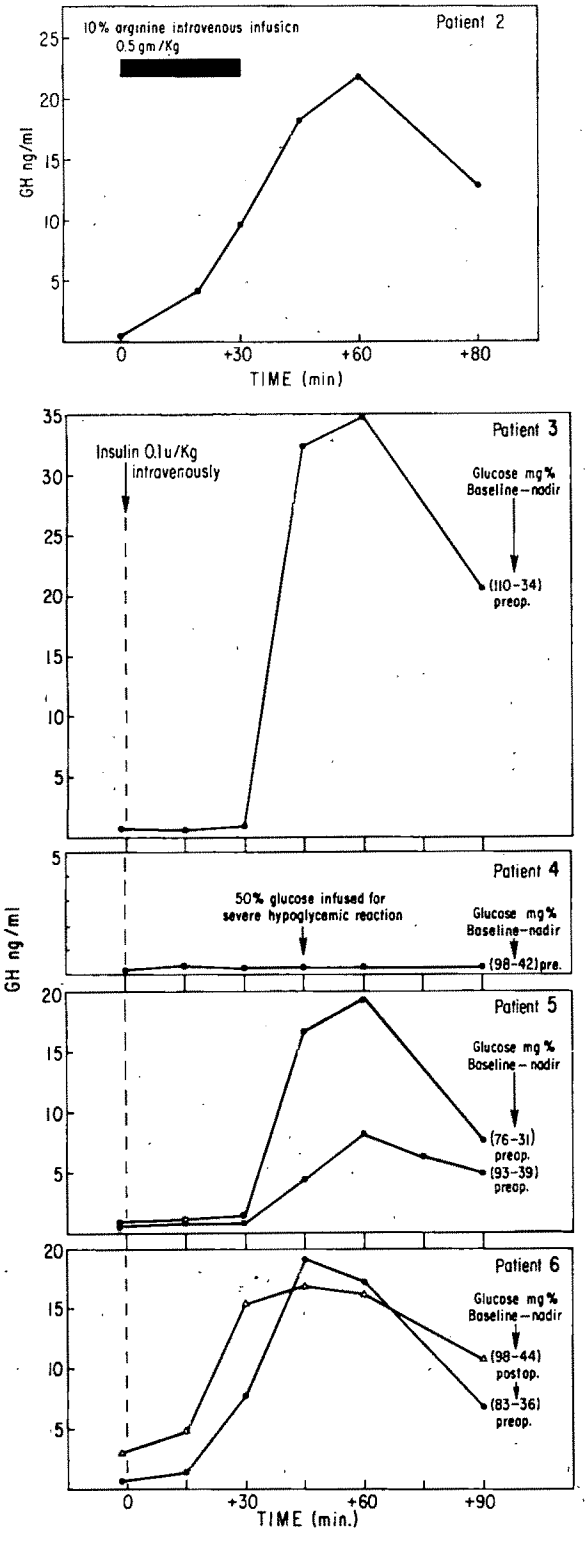


Fig. 3. Growth hormone dynamic testing. Normal GH response to arginine infusion (0.5 gm/kg over 30 minutes) was observed in Case 2. The GH response to insulin-induced hypoglycemia appears completely normal in Cases 3 and 6, absent in Case 4, and impaired in Case 5. Two preoperative tests were performed in Case 5, and the reduced response occurred immediately prior to surgery.

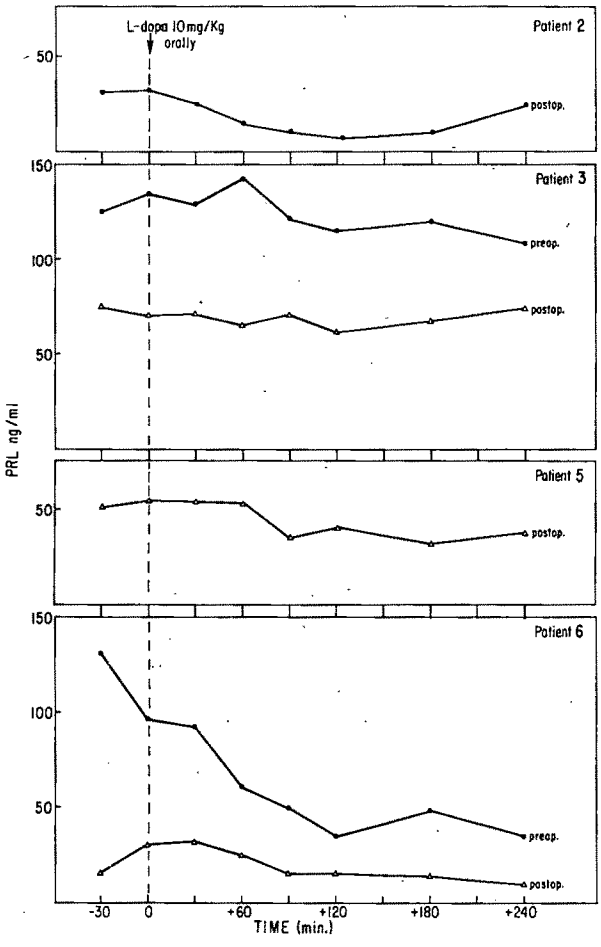


Fig. 4. Serum PRL responses to a single oral dose of of L-dopa (10 mg/kg body weight). Cases 2 and 6 had "normal" responses as defined by a greater than 50% suppression while Case 3 had no significant drop in PRL. A preoperative test was performed in Case 5 but the values remained at approximately 1,000 ng/ml without suppression.

to the pituitary, a tumor which causes sellar enlargement may occasionally undergo spontaneous necrosis, resulting in a partially empty sella.[5] Finally, an intrasellar cyst causing sellar enlargement may rupture, leaving the normal pituitary within an enlarged sella.[20]

The mechanism responsible for elevated serum PRL levels in patients with a herniated, CSF-filled arachnoid diverticulum in the sella remains speculative, but pressure on the pituitary stalk may interrupt prolactin-inhibiting factor transport in a fashion similar to that of stalk section. Since both the pituitary stalk and the diverticulum of arachnoid must pass through the constricting, albeit incompetent, diaphragma sellae, pressure on the pituitary stalk is easily envisioned. Increases in CSF pressure would theoretically be expected further to increase the pressure on the pituitary stalk, explaining the frequent association of factors which increase CSF pressure and an empty sella.[1, 21] The vari-

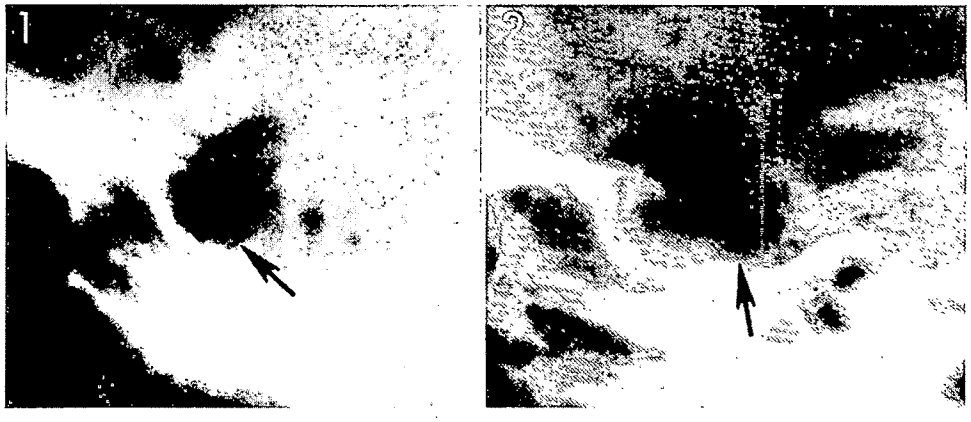


Fig. 5. PEG in Cases 1 and 2, demonstrating air entering the sella (arrows) and confirming the diagnosis of an empty sella secondary to an arachnoid herniation through the diaphragma sellae.

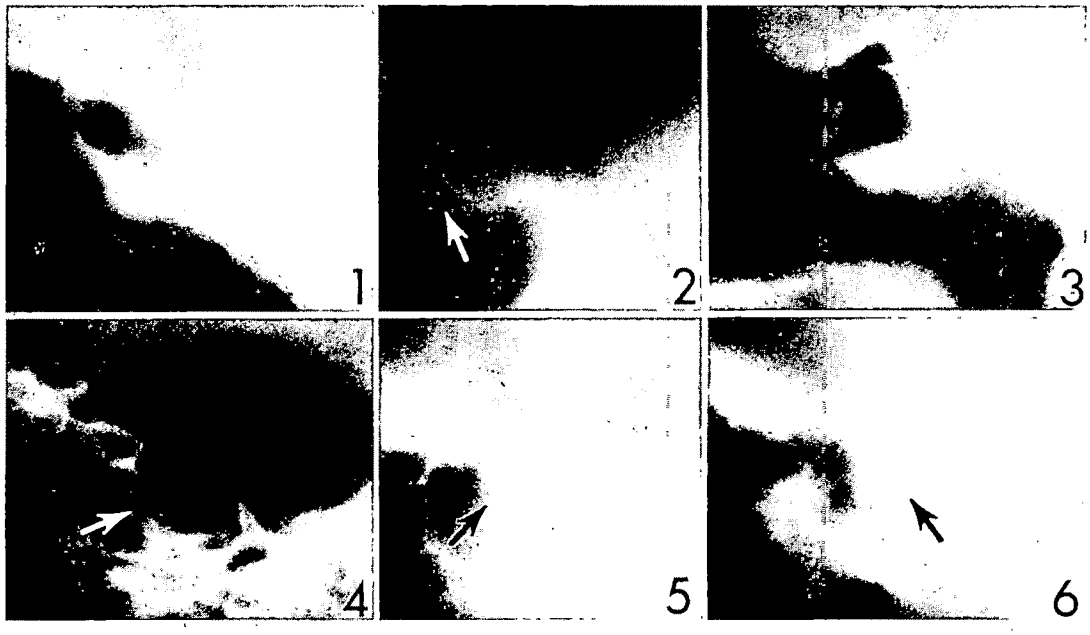


Fig. 6. Tomograms of the sella. Cases 1 and 3 demonstrate symmetric enlargement of the sella while Cases 2, 4, 5, and 6 have more asymmetric enlargement and localized areas of apparent bony erosion (arrows). Trispiral thin-section tomograms are presented for Cases 1, 2, 3, 5, and 6 while the tomogram of Case 4 was obtained by the standard 5 mm tomographic technique.

able loss of trophic hormone function associated with the empty sella syndrome suggests a similar mechanism for other releasing hormone loss. Cases 1 through 4 may represent this clinical situation. Herniation of the arachnoid into the sella was documented by PEG in Cases 1 and 2 and by surgery in Cases 3 and 4. Why PEG failed to demonstrate the arachnoid diverticulum in Cases 3 and 4 is unclear, but this must be considered technical failure.

A PRL-secreting pituitary adenoma which has enlarged the sella may undergo partial ischemic or pressure necrosis with the subsequent findings of hyperprolactinemia secondary to residual adenoma with a coexistent enlarged empty sella. A similar clinical situation has been reported in a patient with spontaneous remission of acromegaly.[5] This appears to be the situation which occured in Case 5, as the PRL level dropped from 1,000 to 64 ng/ml prior to surgery. Unfortunately, the immediately preoperative PRL level was not available until 2 weeks postoperatively and surgical exploration could have been avoided.

Pressure from within the sella, not originating in the pituitary itself, sufficient to permit continued galactotrophic function while compressing the pituitary stalk

against an intact diaphragma sellae, could result in an empty sella and hyperprolactinemia. In Case 6 an expansion of the sella projected inferiorly, simulating tumor erosion. The operative findings seem most compatible with the spontaneous rupture of an intrasellar cyst. Since this patient's sellar enlargement occurred secondary to increased intrasellar pressure with an intact diaphragma sellae, it is not surprising that PEG did not demonstrate air within the sella.

A recent report of the coincidental occurrence of very small pituitary adenomas in association with a partially empty sella[22] raises the possibility that occult microtumors might have escaped surgical detection in one or more of the patients reported here. We are inclined to reject such conjecture, since in five of six patients (Cases 1 to 5) pneumographic or direct surgical visualization revealed a pituitary remnant no more than 3 mm in thickness; furthermore, in each patient operated upon, a small tumor was diligently sought after (with incision and biopsy of the deformed pituitary) without success. Four of our six patients had been symptomatic for 6 to 10 years; to speculate that a true adenoma might achieve less than 3 mm diameter after such an interval requires a new definition of "neoplasia." On the contrary, we are inclined to believe that an uncertain percentage of the "microadenomas" which we, and others, have removed with increasing frequency in the past 5 years may actually represent focal areas of lactotrophic hyperplasia possessing negligible neoplastic potential.

A variety of medications have been associated with mild elevations of PRL.[16, 23] A review of all the medications taken by the patients reported revealed that only the Ortho-Novum-2, Rauzide, and thiothixene taken by the patient in Case 5 have clearly been associated with elevations in PRL. In view of the massive elevation in PRL (1,100 ng/ml) it is unlikely that these agents were responsible.

One or both gonadotropins were elevated in three of the six patients—LH only in Case 6 and both LH and FSH in Cases 1 and 3. In Case 1, the previous gonadectomy probably accounted for the elevation in gonadotropins, the replacement conjugated estrogen being insufficient for suppression. In Case 6, there is no obvious explanation for the single elevated LH value found preoperatively except possible laboratory error. Interestingly, in this patient cyclic menses resumed postoperatively and gonadotropins have remained in the normal range for ovulatory women. In Case 3 FSH and LH levels were persistently elevated both preoperatively and postoperatively. The most reasonable explanation would be a somewhat premature menopause at 38 years of age, but a small gonadotropin-secreting adenoma remains a less likely possibility.

No consistent pattern of trophic hormone loss is associated with an empty sella, but abnormalities in GH response, thyrotropin, and gonadotropins as well as panhypopituitarism have been described.[1–5] Dynamic hypothalamic-pituitary axis testing did not enhance diagnostic accuracy in the six cases presented. This suggests that variable pituitary dysfunction may occur regardless of the etiology of the increased intrasellar pressure.

Expanding intrasellar masses, regardless of origin, enlarge or "balloon" the bony sella turcica, causing upward displacement and osteoporosis of the clinoid processes. Interestingly, two of the four patients with documented CSF-filled arachnoid diverticula within the sella had symmetric enlargement (Cases 1 and 3) while both patients with intrasellar pathology (Cases 5 and 6) had localized erosions. PEG remains an integral part of the evaluation of patients with an enlarged sella as it may distinguish a tumor-filled sella from an empty sella, as well as assess suprasellar extension of tumor. However, the air study may fail to reveal an arachnoid diverticulum within the sella, as demonstrated in Cases 3 and 4. Additionally, transient intrasellar pathology causing sellar enlargement, represented by Cases 5 and 6, may be indistinguishable from pituitary tumor by PEG. Computerized axial tomography appears of limited value in assessing intrasellar disease in the absence of significant suprasellar extension.[16] Unfortunately, none of the currently available endocrinologic or radiographic tests can equivocally distinguish patients with a primary "empty" sella from those with pituitary tumors.

We acknowledge the participation of Dr. Harry T. McPherson in the care of one of the patients.

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Discussion

Dr. Mason C. Andrews, Norfolk, Virginia. The recent availability of serum PRL determinations and the even more recent marketing of bromocriptine for treating PRL excess have vastly increased the interest of clinician and researcher in pituitary adenomas. These adenomas probably occur in 5% to 10% of all women and are almost always asymptomatic. The few which become intolerable "guests," by enlarging sufficiently to damage the surrounding gland and erode surrounding bone, usually take years to do so. They usually signal their presence by amenorrhea, ovulation failure, and frequently galactorrhea. In more than half of these, serum PRL excess provides a useful marker for identification and follow-up. These chromophobe cells seem to be stimulated to multiply and enlarge by increased estrogen such as occurs during pregnancy and, conceivably, medication with oral contraceptives.

The six cases reviewed here were selected from a much larger number managed at Duke University Medical Center which also had x-ray findings of enlargement of the sella turcica, suggesting the presence of an adenoma, and in which an adenoma was found. But these six were eventually found to be different, because the enlarged sella was not occupied by an adenoma at the time diagnosis was made.

It is most important to develop the capability to recognize the difference between a health-threatening adenoma and an empty sella, because operation may potentially produce morbidity and may also result in persistent CSF drainage through the fistula created surgically.

The typical empty sella syndrome involved a defect in the diaphragm above the sella, allowing arachnoid herniation and pressure erosion of the sellar bone along with pressure atrophy of the pituitary gland. Of the six cases, the first four appear to fit this category, and only half of these patients were spared surgery by the radiologic techniques and the endocrine analyses then available.

The vacant space in the sella in the other two appeared more likely to represent the consequence of diminution of a prior cyst or tumor. They too were not spared surgery, because alternative diagnostic techniques proved insufficient. The declining PRL values could have served as a marker in Case 5.

The use of present-generation computer tomography (CT) in several institutions, including our own, seems to offer an avenue for additional information that may reduce the need for the more strenuous PEG, while improving results. The CT scan can detect CSF fluid in the sella especially when the enlargement is moderate or great. The quantity of pituitary hormones in the CSF, obtained by lumbar puncture, may also help to distinguish between tumor and an empty sella.

The surgical treatment of microadenomas is now being approached more conservatively in general. Certain cases may even be treated with bromocriptine in lieu of surgery on an experimental basis. The potential for enlargement during pregnancy should be appreciated.

Perioperative cephalosporin prophylaxis in cesarean section: Effect on endometritis in the high-risk patient

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A total of 120 patients who were to be delivered by cesarean section and who were at high risk of postoperative infection received three doses of either cefamandole, cephalothin or placebo perioperatively. Maternal serum levels for both antibiotics were in the therapeutic range. Although both drugs reduced the incidence of febrile morbidity and endometritis, only cefamandole significantly reduced the fever index. Risk factors for postoperative infections were the presence of ruptured membranes, labor, and internal fetal monitoring. Cefamandole beneficially influenced all risk factors while cephalothin was able to reduce only the risk of ruptured membranes. When a new method for obtaining endometrial tissue was utilized, 50% of cultures were negative. There was no difference in the organisms isolated from patients with and without endometritis. (AM. J. OBSTET. GYNECOL. 134:925, 1979.)

THE RISK OF INFECTION following primary cesarean section is at least ten times that seen after a vaginal delivery; however, an elective repeat cesarean section is not associated with significant febrile morbidity. An operative delivery after labor, ruptured membranes, or internal fetal monitoring is associated with a greater risk of infection.[1] Unfortunately, there is no agreement as to what constitutes risk factors since general anesthesia, preoperative anemia, and obesity also have been implicated in the genesis of postoperative infection. It is also unclear which risk factors can be beneficially influenced by the use of antibiotics.

Several recent studies have shown that a short perioperative course of intravenous antibiotic is as effective as 3 to 5 day therapy in reducing endometritis, wound infection, and febrile morbidity.[2, 3]

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Any agent selected for prophylaxis should be safe, well tolerated, and not a first-line drug for treatment of serious infection. Most members of the cephalosporin family meet these requirements. Cephalothin and cefazolin have been used with variable results in cesarean section.[3-6] Cefamandole, a new semisynthetic cephalosporin, retains activity of the family against common gram-positive organisms but has an expanded spectrum against gram-negative facultative bacilli and some anaerobes. Cefamandole has not been used previously for prophylaxis in cesarean section. Little information is available about antibiotic levels in maternal and cord blood and amniotic fluid when the antibiotic is used for prophylaxis.

Bacteriologic evaluation of the endometrium is technically difficult because of the ease of contamination by endogenous organisms residing in the cervix and vagina. Ledger and colleagues[7] advocated transabdominal endometrial aspiration, but this method would be contraindicated in a patient who has had a recent cesarean section.

The present study compared the effectiveness of cefamandole, cephalothin, and placebo as prophylaxis against infection in a high-risk population undergoing cesarean section. A number of parameters were correlated with endometritis to identify those which contribute to infection and which could be overcome by

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perioperative antibiotics. A new method for endometrial aspiration was used which would theoretically decrease contamination from vaginal and cervical flora. Maternal and cord blood and amniotic fluid antibiotic concentrations were correlated with outcome.

Material and methods

All obstetric patients at the Medical University Hospital between April 27, 1977, and November 16, 1978, became candidates for the study when the decision was made to perform a primary cesarean section. A few patients needing a repeat cesarean section became eligible if they presented with ruptured membranes, labor, extreme obesity, or chronic medical conditions associated with increased risk of infection, such as sickle cell disease or severe diabetes. Reasons for exclusion were signs of infection (oral temperature greater than 100.4° F or clinical amnionitis), known allergy to penicillin or cephalosporins, antibiotic therapy for any reason within the previous 2 weeks, or inability to obtain valid informed consent.

The protocol called for randomized triple-blind allocation of 120 patients into one of three groups. Each patient received either 1 gm of cephalothin,* cefamandole,† or a similar volume of placebo intravenously. The first dose was given on call to the operating room with subsequent doses at two and eight hours after surgery.

Complete blood count, urinalysis, and measurement of serum creatinine levels were performed on each patient before operation and repeated on the second and fourth postoperative days.

Amniotic fluid and maternal and cord blood were sampled at the time of delivery for assay of antimicrobial activity. The blood samples were refrigerated until the serum could be separated by centrifugation. A biologic plate-cup assay, in which the degree of inhibition of susceptible organisms by the patient's serum or amniotic fluid was compared to a simultaneously tested known concentration of cephalothin or cefamandole, was employed to estimate antimicrobial activity; this value was expressed as micrograms of cephalothin or cefamandole per milliliter.

Routine urine cultures were performed on specimens obtained on insertion and removal of the indwelling Foley catheter. Amniotic fluid was cultured at the time of cesarean section for anaerobic and aerobic organisms. Each patient had a uterine aspiration 3 to 5 days after operation to obtain material for culture. All specimens were transported within 30 minutes to the experimental anaerobe laboratory, evaluated by Gram stain, and placed on nonselective media for primary isolation of organisms.

The initial plating of the specimen took place in an anaerobic environment provided by a glove box. Primary isolation of anaerobes was obtained using prereduced, enriched blood agar incubated in a carbon dioxide jar. Anaerobic organisms were identified by means of Gram stain characteristics, gas chromatographic analysis of the end products, and biochemical reactions as determined by the Mini-tec* system. Facultative and aerobic bacteria were identified according to commonly accepted techniques.

A broth dilution assay was utilized to determine the susceptibility of anaerobic bacteria to cefamandole and cephalothin and of aerobic bacteria to cefamandole.[8] Standard agar-diffusion techniques were used to determine susceptibility of aerobic and facultative organisms to cephalothin.[9] Resistance to cefamandole was defined when growth was visible in concentrations of 12.5 μg of cefamandole per milliliter of broth. Resistance to cephalothin was defined as growth in 6.25 μg of cephalothin per milliliter of broth. Standard inhibitory zone sizes were used to determine resistance of aerobic and facultative organisms to cephalothin.

The endometrial aspiration was done by the nurse-co-ordinator with the patient in the lithotomy position. The vagina was swabbed with aqueous Zephiran. The specimens were collected using individually autoclaved, specially modified menstrual aspiration kits† (Fig. 1). After the short outer cannula was placed into the cervix, the inner cannula was inserted into the uterine cavity; endometrial tissue, usually 1 to 5 ml, was obtained under negative pressure with the 50 ml syringe.

Each patient in the study was carefully monitored for signs of infection. Morbidity was defined according to the criteria established by the Committee of Maternal Welfare as an oral temperature of 100.4° F on any 2 of the first 10 postpartum days excluding the first 24 hours. If a patient was considered morbid, appropriate cultures were obtained and the infection was classified under one or more of the following categories: (1) endometritis—fever, uterine tenderness, with or without a positive culture, or fever and a pathogen without other apparent cause; (2) urinary tract infection—fever, urinary tract symptoms, and a positive culture (the infection was subclassified as asymptomatic if a single urine culture obtained post partum contained 100,000 organisms per milliliter after a negative pre-

*Keflin, Eli Lilly & Co.
†Mandol, Eli Lilly & Co.

*Mini-tec, Baltimore Biological Laboratories, Cockeysville, Maryland.
†Rocket of London, Bridgeport, Connecticut.

operative culture and no fever or urinary tract symptoms were present); (3) wound infection—fever, cellulitis, and/or exudate; (4) pulmonary-fever with abnormal x-ray film or physical signs of consolidation. Each infected patient was treated with appropriate antibiotics of the physician's choice, utilizing the results of available cultures and Gram stains.

The fever index[10] was calculated for each patient to quantify clinical response to the short course of antibiotic therapy. Data obtained were subjected to several different statistical analyses.

For the continuous variables one- and two-way analyses of variance were used to estimate and test for mean difference in the placebo and medication groups as well as morbidity and endometritis groups. Relationships between discrete variables were tested utilizing the chi-square test of independence for a contingency table.

A one-way analysis of covariance with dose time as the covariate was utilized in testing for significant mean differences among the placebo and medication groups for the dependent variables cord blood, maternal blood, and amniotic fluid.

Results

There were significant differences with respect to morbidity, endometritis, and fever index (Table I) among the three groups. Although both antibiotics were effective, cefamandole was superior. Endometritis was the major cause of morbidity in each group (Table II).

Although the groups differed in size, they exhibited similar obstetric and demographic variables (Table III). The patients in the stuey reflected the obstetric population served by the hospital—predominantly nonprivate, black, relatively young, and of low parity. All but two of the patients undergoing a repeat cesarean section had either ruptured membranes, active labor, or both.

The placebo group was eliminated after the study was 70% completed because the suspicion of an unacceptably high morbidity rate in that group was confirmed. The remaining patients were allocated in a double-blind fashion to reach a total of 120 evaluable cases. This alteration in protocol was done with permission of both the Institutional Human Research Committee and Eli Lilly & Co. Twenty-one additional patients were not evaluable because they did not adhere to the protocol. There were no adverse reactions to either antibiotic.

Mean cefamandole and cephalothin levels are given in Table IV. No antibiotic activity was present in patients who received placebo. Maternal blood levels were in the therapeutic range for both agents studied, but mean cefamandole levels were twice as high as cephalothin levels. When antibiotic concentrations were corrected for the time of administration, only the maternal blood levels showed a relationship to time; however, a twofold difference between the maternal blood levels of cephalothin and cefamandole remained (Table IV).

All patients who became infected were treated with appropriate antibiotics, usually ampicillin and an aminoglycoside. Half of the 42 patients with endometritis received clindamycin. One noninfected patient in the cephalothin group developed pulmonary emboli requiring heparin therapy. No patient needed an operation for serious postoperative infection. Three patients were readmitted but the only infection-related admission was for acute pyelonephritis 10 days after operation.

The 120 pregnancies included seven sets of twins.

Table I. Comparison of the effect on morbidity between placebo and antibiotic prophylactic groups

	Placebo (N = 29)	*Cephalothin (N = 48)*	*Cefamandole (N = 43)*	*P*
Febrile morbidity (No.)	19	18	–	≤0.05
	19	–	12	≤0.01
	–	18	12	NS
Endometritis (No.)	17	15	–	≤0.05
	17	–	10	≤0.01
	–	15	10	NS
Fever index (mean degree hours)	90.4	68.2	–	NS
	90.4	–	49.5	≤0.01
	–	68.2	49.5	NS

Within each risk factor group, the first P value reflects the difference between placebo and cephalothin; the second P value, the difference between placebo and cefamandole; and the third P value represents the difference between the two antibiotic groups. NS: Not significant.

Table II. Febrile morbidity by cause

Infection	*Placebo (N = 19)*	*Cephalothin (N = 18)*	*Cefamandole (N = 12)*
Endometritis	13	13	9
Endometritis plus bacteremia	3	–	–
Endometritis plus UTI	1	–	–
Endometritis plus pulmonary complication	–	1	
Endometritis plus bacteremia plus wound infection	–	1	1
UTI	2	2	1
UTI plus bacteremia	–	1	–
Wound infection	–	–	1

UTI: Urinary tract infection.

Table III. Epidemiologic and obstetric factors of three medication groups

	Placebo (N = 29)	*Cephalothin (N = 48)*	*Cefamandole (N = 43)*	*P*
Age (yr., mean ± SD)	22.1	21.6	22.7	NS
Status (% service)	100.0	91.6	95.1	NS
Parity (mean ± SD)	0.74 ± 1.63	0.70 ± 1.22	0.81 ± 1.56	NS
Gestational age (wk., mean ± SD)	38.7 ± 3.4	38.1 ± 3.6	39.2 ± 2.0	NS
Race (% black)	86.2	83.3	89.0	NS
Maternal weight (pounds; EG mean ± SD)	161.9 ± 37.0	152.8 ± 31.7	162.2 ± 33.0	NS
Obesity (%)	34	28	35	NS
Repeat cesarean section	13.7	27	16	NS
Duration of labor (hr., EG mean ± SD)	12.1 ± 11.7	10.7 ± 11.8	8.9 ± 11.7	NS
Duration of ROM (hr., EG mean ± SD)	7.7 ± 10.6	7.6 ± 10.5	12.0 ± 26.4	NS
Duration of IFM (hr., EG mean ± SD)	1.6 ± 2.6	1.8 ± 4.6	2.3 ± 3.3	NS
Vaginal examination (mean ± SD)	3.6 ± 2.8	4.1 ± 2.9	3.4 ± 2.6	NS
Estimated blood loss (ml, EG mean + SD)	540.5 ± 231.7	560.9 ± 254.4	586.1 ± 228.4	NS
General anesthesia (%)*	89.1	83.3	76.1	NS
Regional anesthesia (%)*	17.8	28.3	28.5	NS
Primary surgeon (yr. of residency, mean ± SD)	3.6 ± 0.6	3.4 ± 1.0	3.1 ± 1.2	NS
Operating time (min., EG mean ± SD)	68.3 ± 15.5	68.1 ± 16.5	64.3 ± 14.9	NS
Uterine incision–low transverse (%)	78.6	86.3	78.9	NS
Tubal ligation (%)	10.0	12.7	16.0	NS
Transfusion (%)	7.1	10.8	2.0	NS
Postoperative anemia (%)	20.6	29.1	30.2	NS
Postoperative stay (days, EG mean ± SD)	6.0 ± 1.7	6.2 ± 2.7	5.4 ± 1.6	NS
Time of first dose of antibiotic or placebo (min., EG mean ± SD)	55.6 ± 34.6	52.9 ± 39.0	43.4 ± 29.5	NS

EG mean: Estimated group mean; ROM: rupture of membranes; IFM: internal fetal monitoring.
*Some had both general and regional anesthesia.

Table IV. Mean antibiotic activity in maternal blood, cord blood, and amniotic fluid

Prophylactic group	*Time obtained after dose*	*Antibiotic activity (μg/ml) in*		
		Maternal blood	*Cord blood*	*Amniotic fluid*
Placebo	58.3	0*/0.4†	0/.04	0/.05
Cephalothin	45.3	7.5/7.8‡	3.1/3.2§	1.9/1.9§
Cefamandole	56.8	17.1/16.5‡	7.3/7.2§	4.4/4.3§

*Observed antibiotic activity expressed in micrograms per milliliter.

†Calculated antibiotic activity corrected for time.

‡T value, −2.5628, indicates relationship between time and antibiotic levels in maternal blood.

§T values, −0.6463 and −1.3772, indicate no relationship.

Table V. A comparison of positive amniotic fluid cultures in patients with endometritis in the three medication groups

Medication	*Endometritis*	*No endometritis*	*P*
Placebo	4*/14	2/9	NS
Cephalothin	1/14	1†/27	NS
Cefamandole	0/10	3‡/23	NS

*The same organism as that in amniotic fluid was cultured from endometrium or blood in three.

†The same organism was also cultured from endometrium.

‡One culture of the same organism from endometrium.

Two unsuspected intrauterine fetal deaths, each occurring in one of twins, were a result of underlying hypertensive disease. Two neonatal deaths occurred in low–birth-weight infants (less than 1,021 grams) delivered for maternal indications unrelated to infection. No infant in the study developed problems from intrauterine exposure to antibiotics or masked infections.

Twenty-one patients with previous cesarean sections were included in the study. None of the four who received placebo or the seven given cefamandole developed endometritis while five of the 10 who received cephalothin did so. In the placebo group, a repeat cesarean section was protective against endometritis ($p < 0.01$) even if ruptured membranes or labor was present. No common factor could predict risk for endometritis following a repeat cesarean section in the cephalothin group; four of the patients with endometritis experienced labor, two had ruptured membranes, and one had a twin pregnancy.

Bacteriology. Eleven of 97 amniotic fluid cultures were positive (Table V), all but three for anaerobes only. Endometritis developed after a positive amniotic fluid culture in four of six patients, one of two patients, and no patients in the placebo, cephalothin, and cefamandole groups, respectively. The same organism that was recovered from amniotic fluid was also isolated from blood or endometrium in three patients who re-

Table VI. A comparison of positive endometrial cultures in patient with and without endometritis in the three medication groups

Medication group	*Endometritis*	*No endometritis*	*P*
Placebo	9/17*	6/9	NS
Cephalothin	9/15	14/27	NS
Cefamandole	2/10	13/29	≤0.001
Totals	20/42	33/65	NS

*Number positive in total number of cultures.

Table VII. Types of organisms associated with specific infectious disease

Category	*Associated organisms*	*Frequency of isolation*	
		Infected patients (N = 25)*	*All others (N = 44†)*
Endometritis	*Bacteroides*	16‡(67)§	18(40)
	Fusobacterium	0(0)	5(11)
	Anaerobic cocci	7(29)	12(27)
	Clostridium	1(4)	3(7)
	Eubacterium	1(4)	2(4)
	Enterobacteriaceae	4(17)	11(25)
	Staphylococcus	1(4)	3(7)
	Streptococcus	0(0)	6(14)
	Enterococcus	2(8)	7(16)
	Other	1(4)	2(4)
Bacteremia and endometritis	*Bacteroides*	2	–
	Fusobacterium	1	–
	Anaerobic cocci	2	–
	Staphylococcus	1	–
	Streptococcus	1	–
Urinary tract infection	*E. coli*	1	4
	Enterococcus	3	0
Wound infection	*Proteus mirabilis*	1	0

*N = number of infected patients with positive cultures.

†N = number of noninfected patients with positive cultures.

‡Number of strains isolated.

§Frequency of isolation from patients with positive cultures (N) expressed as percent.

ceived placebo; these were *A. fermentans, Bacteroides* species, and *B. melaninogenicus.* One paired positive culture occurred in both the cephalothin and cefamandole nonmorbid groups; the organisms were *B. melaninogenicus* and *S. intermedius* in each group, respectively.

Fifty-four of the 107 (50.4%) endometrial cultures were negative (Table VI). There was no correlation between a negative endometrial culture and the presence or absence of endometritis. Fewer positive cultures were obtained from patients with endometritis who received cefamandole; all organisms isolated in these patients were anaerobes. In general, those patients with endometritis on each medication showed fewer species of organisms.

Table VIII. Antibiotic susceptibility of microorganisms recovered from all cultures

	Susceptibility of microorganisms according to category							
	Aerobes				*Anaerobes*			
	S		*R*		*S*		*R*	
Antibiotic	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
Cephalothin	39	60	26	40	64	74	23	26
Cefamandole	45	75	14	24	62	80	16	20

S: Sensitive; R: resistant.

Table IX. Differential resistance to prophylactic antibiotics of microorganisms obtained from patients in each prophylactic group.

Prophylactic group	*Organisms resistant to*			
	Cephalothin		*Cefamandole*	
	No.	*%*	*No.*	*%*
Placebo	9/37*	24	6/37	18
Cefamandole	12/28	43	14/28	50
Cephalothin	14/41	34	4/41	10

*No. resistant/total no.

The types of organisms associated with specific infectious morbidity were compared to the organisms cultured from uninfected patients (Table VII). Undisputable pathogenic organisms were *Bacteroides, Fusobacterium,* anaerobic cocci, *Staphylococcus,* and *Streptococcus,* which were cultured from the blood of five patients with endometritis. The organisms cultured from the endometrial cavity were the same in infected and noninfected patients; however, the frequency of isolation of each organism except for *Bacteroides* was greater from the noninfected patient's uterine cavity. *E. coli* was a common urinary tract contaminant but was responsible for only one urinary tract infection while enterococcus was the causative agent in three urinary tract infections.

The susceptibility of the microorganisms to the cephalosporins used as prophylactic agents is shown in Table VIII. Cefamandole, when compared to cephalothin, has an expanded spectrum for both aerobes and anaerobes. The improved antimicrobial activity of cefamandole is especially noticeable when aerobic bacteria are considered (Table VIII).

Analysis of the effect of prophylactic antibiotics on

Table X. Comparison of risk factors present in patients with endometritis

Risk factor	*Placebo*	*Cephalothin*	*Cefamandole*	*P value*
Labor (%)	63.4	38.2	–	NS
	63.4	–	17.8	≤0.0009
	–	38.2	17.8	NS (0.07)
ROM (%)	70.0	28.5	–	≤0.004
	70.0	–	14.8	≤0.0001
	–	28.5	14.8	NS
IFM (%)	66.7	33.3	–	NS
	66.7	–	23.5	≤0.02
	–	33.3	23.5	NS
Obesity (%)	60.0	66.7	–	NS
	60.0	–	26.6	NS
	–	66.7	26.6	≤0.03
Anemia (second postoperative day) (%)	66.6	53.8	–	NS
	66.6	–	41.6	NS
	–	53.8	41.6	NS
General anesthesia (%)	58.0	35.0	–	NS
	58.0	–	27.0	NS
	–	35.0	27.0	NS

Within each risk factor group, the first P value reflects the difference between placebo and cephalothin; the second P value, the difference between placebo and cefamandole; and the third P value represents the difference between the two antibiotic groups.

Table XI. Comparison of risk factors present in patients with febrile morbidity

Risk factor	*Placebo*	*Cephalothin*	*Cefamandole*	*P value*
Labor (%)	68.1	44.1	–	≤0.07
	68.1	–	25.0	≤0.002
	–	44.1	25.0	NS
ROM (%)	70.0	35.7	–	≤0.01
	70.0	–	18.5	≤0.0004
	–	35.7	18.5	NS
IFM (%)	66.6	41.6	–	NS
	66.6	–	29.4	≤0.04
	–	41.6	29.4	NS
Obesity (%)	60.0	66.6	–	NS
	60.0	–	26.6	NS
	–	66.6	26.6	≤0.03
Anemia (second postoperative day) (%)	66.6	50.0	–	NS
	66.6	–	46.1	NS
	–	50.0	46.1	NS

Within each risk factor group, the first P value reflects the difference between placebo and cephalothin; the second P value, the difference between placebo and cefamandole; and the third P value represents the difference between the two antibiotic groups.

the resistance to each drug shows that in patients receiving cefamandole organisms are more frequently resistant to both antibiotics while the organisms recovered from patients receiving cephalothin are more likely to be resistant to that agent but not to cefamandole (Table IX).

Risk factors. Analysis of over 50 variables was carried out to ascertain the relationship of these to differences in morbidity and endometritis in placebo and medication groups. Those variables in which there was a clustering of ill patients found were labor, prolonged rupture of membranes, internal fetal monitoring, multiple gestations, and abnormal presentations. Only the first three were statistically significant risk factors (Tables X and XI). The number of vaginal examinations, anemia, and obesity were similarly analyzed but were not risk factors for our patients.

General anesthesia was not a significant risk factor; most patients in the study received a general anesthetic with only one case of atelectasis in the postoperative period. Twenty-one patients had regional anesthesia for the cesarean section (18 epidural and three spinal). One patient in each antibiotic group and two of the three who received placebo developed endometritis as did two of six patients who had general anesthesia to supplement an epidural anesthetic.

Green and Sarubbi[11] categorized patients as low risk if they had only one risk factor present and high risk if they had two or more present. With general anesthesia included among the other variables (obesity, anemia,

prolonged ruptured membranes, labor, and internal fetal monitoring) only 18 of 120 patients were classified as low risk, and there was no correlation with the presence or absence of endometritis or febrile morbidity. After general anesthesia was removed as a risk factor in this analysis for the reasons described above, only 28.5% of the placebo group with one risk factor developed endometritis as opposed to 70% of those with two or more ($p \leq 0.05$).

When the variables of anemia and obesity in addition to general anesthesia were removed, only 28% of the placebo group with one risk factor developed endometritis as opposed to 72% of those with two or more ($p \leq 0.01$).

When cephalothin was compared to placebo, only the risk effect of a longer duration of ruptured membranes could be overcome by administration of that antibiotic ($p \leq 0.004$). When cefamandole was compared to placebo, the antibiotic was highly effective in reducing the risk from prolonged ruptured membranes ($p \leq 0.0001$) and longer duration of labor ($p \leq 0.0009$), and also was effective against the effect of internal monitoring ($p \leq 0.02$). When the two antibiotics were compared, fewer patients were infected in the cefamandole group but the differences were not statistically significant.

Comment

Both cefamandole and cephalothin are effective in reducing febrile morbidity and endometritis following cesarean section in a high-risk population; cefamandole is also effective ($p \leq 0.01$) in reducing fever index (Table I). Endometritis with or without bacteremia, urinary tract infection, and wound infection remain the major causes of postoperative febrile morbidity. The present findings differ from our previous study[6] in which cefazolin was bacteriologically but not clinically effective in reducing post–cesarean section febrile morbidity. The difference in results might be accounted for, in part, by the fact that repeat cesarean section patients were excluded from the present study unless they had ruptured membranes, labor, or significant underlying medical conditions. No patient undergoing repeat cesarean section who received either placebo or cefamandole developed endometritis, even in the presence of labor or prolonged ruptured membranes. The protective effect of a repeat cesarean section does not hold true in the group of patients who received cephalothin; the finding that five of 10 patients in that group developed endometritis cannot be explained.

The present study compared favorably with other reports using a single agent in a short perioperative fashion. Cefamandole levels were twice as high as cephalothin levels in all areas examined. The serum levels (maternal) were in the expected range based on dosage and elapsed time between administration and sampling. One must assume the therapeutic levels of 15 to 20 μg/ml of cephalothin and cefamandole were obtained at the end of intravenous infusion of the drugs at about the time of cesarean section.[12] No patient in the present series developed an allergic reaction to the medication received or had masked serious postoperative infection. Thus, neither prolonged antibiotic prophylaxis nor the use of multiple agents appears justified.

None of the infants was infected. The neonatologists were aware of the study and did not feel hampered in evaluating potential neonatal problems following the exposure to one dose of a cephalosporin before delivery.

Fifty-four of 107 endometrial cultures obtained using a new double-lumen catheter via a transvaginal approach were bacteriologically sterile. These results are similar to those achieved by Ledger and colleagues[7] with transabdominal uterine cultures in patients with endomyometritis after vaginal delivery. In their series 36.8% of transabdominal cultures were positive as compared to 96% of transvaginal cultures in the same patients. A transabdominal culture would be contraindicated in patients 2 to 4 days after a cesarean section. An additional fact which supports reduced cervical and vaginal contamination of specimens obtained through the new collecting system is that fewer species of organisms per patient were recovered, even in the placebo group. Only 109 strains were isolated from the 107 cultures which is a reduction in number from those we obtained postoperatively in our previous study[6] and those reported by others.[13] The most prevalent organisms isolated, *Bacteroides* species, anaerobic cocci, and *Enterobacteriaciae*, are the same as those previously reported by Ledger and colleagues and Gibbs and associates.[13] Although the results with the new collecting system look promising, further evaluation and direct comparative study are necessary.

As previously noted by Gibbs and associates,[13] there was no difference in the organisms isolated from patients with or without endometritis. This may reflect the fact that endometritis is predominantly a clinical diagnosis based on fever and uterine tenderness with abnormal lochia. Further work is necessary in the area of host-bacteria interaction to find out why pathogenic organisms in the endometrium of some patients do not lead to infection. Possibly, the organisms in some of the infected patients are deep within the myometrium and not amenable to sampling through currently available

techniques. Perhaps the absolute number of organisms present would correlate with infection.[14]

The lack of association between positive amniotic fluid cultures and later endometritis had previously been noted by Wong and co-workers.[3] In his study, the antibiotic was not administered until after the cord was clamped, so it is reasonable to expect that no antibiotic was present in the amniotic fluid. This might have accounted for the higher number (39 of 45) of positive cultures in patients without postoperative infectious morbidity. Our data suggest the organisms cultured from amniotic fluid could be useful in predicting the causative agent of endometritis and bacteremia. In the present study only anaerobes were isolated from patients who had received cefamandole; these organisms were present in only a few cases, and none of the patients developed postoperative endometritis. This possibly reflects both the antibacterial spectrum and the greater concentration of that antibiotic within the amniotic fluid.

The different pattern of antibiotic resistance in organisms isolated from patients who received cefamandole (Table IX) may be accounted for in several ways. Cefamandole may favor selection of strains whose mechanism of resistance is due to factors other than beta-lactamase production.[15] These strains might be permeability mutants and therefore resistant to cephalothin also. On the other hand, beta-lactamase production plays a role in the resistance of organisms selected by cephalothin administration, and these would not be resistant to cefamandole, which is not easily hydrolyzed.

The presence of risk factors which influence cesarean section morbidity must be considered in the proper utilization of prophylactic antibiotics. Green and Sarubbi[11] postulated that obesity, anemia, general anesthesia, and prior labor were the significant variables influencing postoperative fever and infection. In a prospective study Green and co-workers[2] found that the use of short-course perioperative prophylactic ampicillin reduced morbidity from 63% to 15% in the high-risk group (two or more risk factors present) while 25% of untreated low-risk patients had febrile morbidity.

Gibbs and colleagues[16] challenged these risk factors and stated that labor, ruptured membranes, and the number of vaginal examinations were most significant. Internal fetal monitoring was not a risk factor for infection beyond that already imposed by the presence of labor and ruptured membranes. They reported that general anesthesia and obesity were not risk factors.

The 129 patients in whom the risk factors were originally established by Green and Sarubbi were distributed as follows: private, 42%; white, 52%; and regional anesthesia, 36%. Our patient population resembles that of Gibbs and co-workers—primarily indigent, nonwhite, and likely to receive general anesthesia. Common risk factors seen in both groups include ruptured membranes and the presence of labor; we also cannot be sure if internal fetal monitoring is in itself a risk factor. There was no significant difference between the number of vaginal examinations in patients who became infected as opposed to those who did not. Anemia, obesity, and general anesthesia were not risk factors in our patient population. A repeat cesarean section appears to be protective against the development of postoperative endometritis even if ruptured membranes, labor, or both are present, and the procedure is no longer elective.

Risk factors must be assessed for the population served. In our patients, administration of cephalothin was effective only in overcoming the risk of ruptured membranes. The administration of cefamandole when compared to placebo significantly reduced the risks of labor, ruptured membranes, and internal fetal monitoring. The administration of either antibiotic significantly reduced the incidence of postoperative febrile morbidity and endometritis, but only cefamandole significantly reduced the fever index.

Conclusions

1. Both cephalothin and cefamandole significantly reduced the incidence of postoperative febrile morbidity and endometritis; cefamandole significantly reduced the fever index ($p \leq 0.01$).
2. Risk factors for postoperative endometritis and febrile morbidity were the presence of ruptured membranes, labor, and internal fetal monitoring.
3. Obesity, general anesthesia, and anemia were not risk factors in our patients.
4. Cefamandole was able to reduce all of the risk factors while cephalothin was able to overcome only the effect of ruptured membranes.
5. There were no differences in the organisms isolated in patients with and without endometritis.
6. When a new endometrial sampling technique was used, 50% of cultures were negative.

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Discussion

DR. SAMUEL M. GOODRICH, Milledgeville, Georgia (Official Guest). Antibiotic prophylaxis implies the preventive use of antibiotics where contamination might occur but is not yet present. Once contamination occurs, then antibiotic administration should be considered therapeutic. Burke[1] summarized five principles to be considered in using prophylactic antibiotic therapy:

1. The effectiveness of defense against bacteria depends largely on natural host resistance.

2. The abnormal physiology induced by anesthesia and operation reduces host resistance.

3. Infection can be prevented or reduced by supplementing host antibacterial resistance but the supplement must be delivered before bacterial contamination of the tissue occurs.

4. Supplements to host resistance serve no purpose in prevention if they are given for periods longer than 4 hours after the end of active bacterial contamination of tissue or bloodstream.

5. Preventive antibiotic supplement should be used only if the risk of infection is clearly greater than the risks of side reaction to the preventive antibiotic.

Chodak and Plant[2] reviewed the English literature over a 16 year period from 1960 to 1976, on the subject of prophylaxis with systemic antibiotics in surgery. Of 131 articles, only 24 met the criteria of an appropriately designed study that generated evaluable data. Major faults in experimental design included: (1) inadequate controls, (2) failure to randomize patients, and (3) failure to begin prophylaxis preoperatively. Even when the studies were well designed, some could not be evaluated because of inappropriate antibiotics, imprecise definition of wound infection, study of nonhumans, and selective removal of more than 15% of patients. Chodak and Plant concluded that those forms of surgery where prophylaxis is clearly of value include hysterectomy, cesarean section, Charnley total hip operations, and microsurgical craniotomies.

There seems to be general agreement that properly administered prophylactic antibiotics reduces febrile morbidity in patients undergoing cesarean section.[3, 5, 7, 8] The incidence of urinary tract infections, wound infections, and serious postoperative pelvic infections is not decreased.[7] The patient undergoing a repeat cesarean section, not in labor, and with intact membranes is considered to have a low risk of developing febrile morbidity. However, there appear to be different high-risk factors when papers from various institutions are studied.[3, 5, 7, 8]

In 1977, Green and Sarubbi[4] published a study identifying four risk factors, which in their institution are associated with post–cesarean section febrile morbidity. These factors were discussed in the paper just presented. If at least two of the factors were present, they could identify 87% of patients who would develop febrile morbidity.

Then, in a study treating those high-risk patients meeting at least two of these criteria, they demonstrated a significant reduction in febrile morbidity. However, in a recent study by Kreutner and coworkers,[6] no reduction in febrile morbidity by using perioperative antibiotic prophylaxis could be demonstrated. However, 43 of the 97 patients were undergoing repeat cesarean sections and would be expected to be in a low-risk group. Also, they did not find the Green and Sarubbi[4] criteria for high risk to correlate with febrile morbidity in their patients. Gibbs and coworkers[3] did not find general anesthesia or obesity to be high-risk factors in their patients.

It seems from these observations that it is not realistic for one institution to use another hospital's criteria for

high risk. Each institution should determine its own high-risk factors, since there will be differences in microbiologic population, patient population, and surgeons.

The present study by Kreutner and associates differs from the earlier study by demonstrating the effectiveness of prophylactic antibiotics. However, I am concerned about this being a blind study if it could be recognized that the placebo group had unacceptable febrile morbidity before the study was completed. Also, the removal of 21 patients from the study, due to failure to meet protocol, is equivalent to exclusion of 15% of the potential study population.

In studying the effects of labor, ruptured membranes, and number of pelvic examinations, how accurate are these estimates? Are all pelvic examinations during labor charted? If membranes rupture out of the hospital, can this time be accurately determined?

In this study, Kreutner stated that a few patients requiring repeat cesarean section became eligible for study if they presented with ruptured membranes, labor, extreme obesity, or medical conditions associated with increased risk of infection. These 21 patients amount to 17.5% of the study group. There are no data presented indicating that the duration of exposure to such variables as ruptured membranes, labor, or internal fetal monitoring can be correlated to the occurrence of febrile morbidity. If membranes are ruptured over 24 hours, should we consider prophylactic antibiotics or therapeutic antibiotics? I suspect that the duration of ruptured membranes and labor would be much shorter in the group of patients undergoing repeat cesarean section.

I am reluctant to accept the statement that a placebo was protective against endometritis in repeat cesarean section. This is based on four patients in the placebo group, none of whom developed endometritis. I suggest if the data in the repeat cesarean section groups indicate anything it would be that antibiotic prophylaxis is of little benefit in this group of patients. Again it would be interesting to examine data presenting the duration of exposure to ruptured membranes and labor.

I was pleased to note that this study also investigated the clinical course of the infants delivered by cesarean section. It would be interesting to know of the course of the infants whose mothers developed febrile morbidity.

Finally, we must never forget that antibiotic prophylaxis is a supplement but not a replacement for following good surgical principles and technique.

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DR. W. SIEGFRIED SMITH, JR., Greensboro, North Carolina (Official Guest). The present-day practice of obstetrics has seen the emergence of invasive techniques of monitoring the fetus which provide us with a more accurate assessment of the fetus during labor. Accompanying this has been a trend for an increase in the cesarean section rate. Because of the increase in the cesarean section rate and invasive monitoring, there has been an increase in morbidity and specifically endometritis. As a result, numerous studies have been undertaken to decrease the incidence of postpartum febrile morbidity by employing prophylactic antibiotics in cesarean section.[1-3]

Sweet and Ledger[4] reported the incidence of antepartum amnionitis and postpartum endometritis in a prospective study of 6,436 deliveries as 3.8%. This patient population consisted of indigent patients and private patients. The incidence of endometritis following cesarean section was increased to 13% in the private group and 27% in the indigent group. Wong and colleagues[3] recently reported the incidence of uterine infection following cesarean section in patients with invasive fetal monitoring as 40.4% compared to 20.4% in a group of patients undergoing cesarean section without invasive fetal monitoring.

Clearly there are questions which need to be answered concerning postpartum infection in cesarean sections and fetal monitoring. Some of the questions which we might ask are: Which patients do or do not need antibiotics? How does one select the patient who may be helped by antibiotics? Which antibiotics does one use? For how long should they be used? What is the bacterial flora of the endometrium?

Green and Sarubbi[5] listed four risk factors which they considered important in identifying the patient at risk of postpartum infection. They concluded that febrile complication occurred four times more frequently in patients with two or more of these risk factors than in those patients with less than two risk factors. Their factors included general anesthesia, obesity, hematocrit of 30% or less, and labor prior to delivery. This study indicated that general anesthesia and obesity are not risk factors, which supports the data from Gibbs and co-workers[6] who found that general anesthesia and obesity did not seem to be major determinants of infection.

Gibbs and co-workers[6] feel that the factors to be con-

sidered are rupture of membranes, labor, internal fetal monitoring, and vaginal examinations. Statistically they calculated that internal fetal monitoring was the least important. Vaginal examination and rupture of membranes were felt to be twice as important as internal fetal monitoring and the duration of labor was calculated to be four times as important.

Gassner and Ledger[7] stated that infection rates in elective repeat cesarean section were 5% as compared to 40.4% and 20.4% for patients in labor who were or were not monitored. Both Gibbs and co-workers[6] and Gassner and Ledger[7] feel that internal fetal monitoring in itself is not the cause of increased infection, but it indicates those patients who have longer labors, longer intervals of ruptured membranes, and more vaginal examinations. This paper indicates that there was no significant difference between the number of vaginal examinations in patients who became infected and those who did not. The length of labor needs to be clarified further to assess accurately its role as a risk factor.

The incidence of endometritis in this series was 58.8% in the placebo group compared to 31.2% with cephalothin and 23.2% in the Mandol group. The incidence of endometritis in the placebo group when general anesthesia was eliminated as a risk factor was 28.5% in those with one risk factor and 70% in those with two or more risk factors. This compares with most series and further emphasizes the fact that there are multiple factors to be considered in selecting patients who are at high risk of infections.

That antibiotics are effective in reducing postpartum morbidity and postpartum endometritis seems to be clear from a review of different antibiotic regimens.[1-3, 8-12] Which regimen to use is more difficult. The infection rate in this series of 58.5% in the placebo group and 31.2% and 23.2% with antibiotics compares to the series of Gibbs and colleagues[2, 10] who reported an overall morbidity rate of 63% in the placebo group compared to 25% in the treated group. Multiple regimens of antibiotics including penicillin-kanamycin and clindamycin-kanamycin have been used. The evidence here indicates that a short course of an intravenous, perioperative cephalosporin is quite effective in decreasing the incidence of endometritis.

I support the authors in the use of cephalosporin as a prophylactic antibiotic when used perioperatively for a short term in order to reserve penicillin, kanamycin, and clindamycin for those patients who do develop endometritis. The treatment of Gibbs and colleagues[13] of postpartum endometritis would be suitable for those patients who develop postpartum endometritis even though they received a cephalosporin as a prophylactic antibiotic.

Since anaerobic cultures are not easily obtained at most hospitals the bacteriologic data are important to the practicing obstetrician. Reports vary somewhat but the predominant organisms which consistently appear are *Bacteroides,* anaerobic cocci, *Streptococcus,* and *Escherichia coli.*[2, 3, 9, 11]

In summary this paper supports the hypothesis that a short-term course of a cephalosporin does increase the incidence of endometritis in cesarean section. General anesthesia, obesity, anemia, and vaginal examinations do not appear to be high-risk factors. Labor, fetal monitoring, and rupture of the membranes need further examination as to their relative risk in infection. A general idea of the bacteriology one can expect to encounter in most cases of endometritis has been provided. Most important, it has been emphasized that prophylactic antibiotics are not a panacea and the incidence of postpartum infection in cesarean section patients treated with prophylactic antibiotics is still in the range of 20% to 30%.

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Identification of differing etiologies of clinically diagnosed premature menopause

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Investigations were performed in eight young women to determine if the findings of secondary amenorrhea and high follicle-stimulating hormone levels were due to primary ovarian follicular atresia or to other causes. Karyotypes were determined from both peripheral leukocytes and ovarian tissue; one woman had XXX/XX/XO mosaicism. Another woman had normal ovarian histology and probably had the "gonadotropin-resistant ovary syndrome." No autoimmune antibodies were detected, but one woman with myasthenia gravis also had ovarian histology that demonstrated primary ova and a developing follicle. Only five of eight women had primary ovarian follicular atresia, and two of the other three women had conditions theoretically compatible with subsequent pregnancy. (AM. J. OBSTET. GYNECOL. 134:936, 1979.)

PREMATURE MENOPAUSE is defined as ovarian failure with cessation of menses occurring prior to the age of 40 years. In both premature and normal menopause, the usual cause for these changes is ovarian follicular atresia with greatly reduced ovarian estrogen production. As a result of the lack of negative estrogen feedback from the ovarian follicles to the hypothalamic-pituitary area, there is increased follicle-stimulating hormone (FSH) production, resulting in high blood and urine FSH levels that are useful in the diagnosis of menopause (either normal or premature) and in distinguishing it from other causes of amenorrhea.

In this investigation, we sought to determine if a group of young women with premature menopause all had ovarian follicular atresia or if other conditions existed which were associated with high FSH levels and secondary amenorrhea.

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Material and methods

The eight women studied were between 22 and 34 years of age, and all had elevated serum gonadotropin levels plus amenorrhea. All women had experienced spontaneous menses in the past, had given informed consent for the experimental parts of the study, and had a history of between 2 and 12 years of amenorrhea. There had been only one pregnancy in the group, and this had resulted in spontaneous abortion. All participants had normal sella turcicas by x-ray films and normal blood levels of serum free thyroxine.

Serum FSH and luteinizing hormone (LH) were determined by radioimmunoassay[1, 2] in which FSH values over 70 mIU/ml were considered postmenopausal. Total urinary gonadotropin excretion was determined by bioassay[3] in which a postmenopausal level consisted of over 50 mouse uterine units (muu)/24 hours. Estrogen status was assessed by the maturation index of vaginal cells and by 24 hour urine estrogen excretion determined by Brown's[4] method.

Karyotypes were determined after a modification of the method of Moorehead and colleagues[5] for both peripheral blood and tissue removed from the ovaries at the time of biopsy. Histologic examination of the ovaries was done in all cases. The tissue was obtained by laparoscopic biopsy in seven instances and by

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Table I. Clinical data in eight young women with secondary amenorrhea and high FSH levels

Case No.	Age (yr.)	Age at menarche (yr.)	Duration of amenorrhea (yr.)	History of hot flashes	Height	Weight (pounds)
1	24	20	2	No	5′5″	114
2	27	15	12	No	5′7″	126
3	22	13	2	Yes	5′4″	141
4	34	17	3	No	5′5″	157
5	23	16	7	No	5′2″	125
6	23	13	6	No	5′7″	111
7	29	10	11	Yes	5′2″	201
8	30	11	12	No	4′11″	115

Table II. Endocrine data in eight young women with secondary amenorrhea and high FSH levels

Case No.	Serum FSH (mIU/ml)	Serum LH (mIU/ml)	Urinary gonadotropins (muu/day)	Urinary estrogens (mcg/day)				Vaginal maturation index (parabasal/ intermediate/superficial)
				Estrone	Estradiol	Estriol	Total	
1	149	86	50-100	—	—	—	11	80/20/0
2	124	74	16-50					0/10/90
	207	72	>100	2	3	7	12	30/70/0
3	310	182	>100	13	<1	<1	13	0/100/0
4	302	68	>100	5	7	15	27	0/50/50
5	177	55	>100	1	1	16	18	0/90/10
6	309	203	>100	4	3	45	52	100/0/0
7	127	79	>100	—	—	—	—	0/90/0
8	137	80	50-100	13	1	<1	14	35/65/0

Table III. Histologic, cytogenetic, and autoantibody data in eight young women with secondary amenorrhea and high FSH levels

Case No.	Ovarian histology	Karyotype		Autoimmune antibodies	
		Peripheral leukocytes	Ovary	Antiovary antibody	Antinuclear antibody
1	Rare follicle and no ova or cysts seen. Stroma compact and focally fibrotic	47,XXX 45,XO	47,XXX 46,XX 45,XO	Neg.	Neg.
2	Normal ovarian tissue	46,XX	46,XX	Neg.	Neg.
3	Normal ovarian tissue	46,XX	46,XX	Neg.	Neg.
4	Rare follicle and no ova or cysts seen. Stroma compact with fibrotic capsule	46,XX	46,XX	Neg.	Neg.
5	No ova, cysts, or follicles. Stroma compact	46,XX	46,XX	Neg.	Neg.
6	Rare follicular and germical cyst and no ova seen. Stroma compact	46,XX	46,XX	Neg.	Neg.
7	No ova, cysts or follicles. Stroma compact	46,XX	46,XX	Neg.	Neg.
8	Rare ova, no cysts or follicles. Stroma compact	46,XX	46,XX	Neg.	Neg.

laparotomy in one case. The tissue was stained with hematoxylin and eosin and evaluated by light microscopy by a single examiner.

Serum from each patient was examined for the presence of autoimmune antibodies by a modification of the method of Coon and associates[6] of indirect immunofluorescence utilizing rat liver for antinuclear antibody and human corpus luteum for anti–theca interna antibody.

Results

Clinical data and the results of various examinations are shown in Tables I, II, and III. Three cases which are different from the remaining five are reviewed below.

Case reports

Case 1. A 24-year-old woman, gravida 0, noted the beginning of breast development at about age 12, and

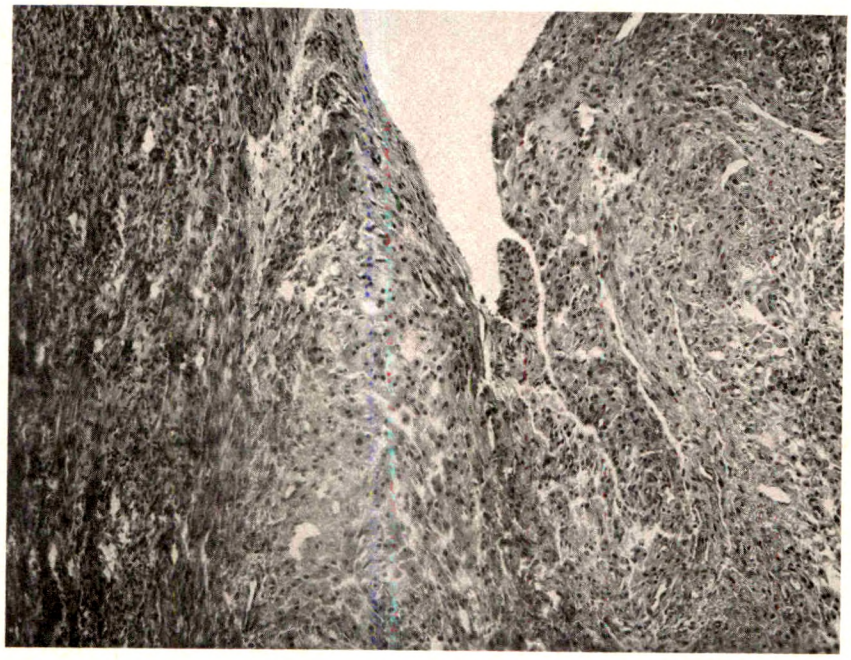


Fig. 1. Ovarian tissue from Case 2 obtained by laparoscopic biopsy. Note normal ovarian tissue with an involuting corpus luteum. (Hematoxlin and eosin. Original magnification ×100.)

axillary hair development at around age 18. At 18, she experienced her only spontaneous menses, although subsequent episodes of vaginal bleeding were induced with estrogen and progestin. When the patient was 20 years old, a bioassay for total urinary gonadotropins was between 6 and 16 U/24 hours (a normal value). A buccal smear showed 32% of cells having a single Barr body and 5% having double Barr bodies.

At age 24, blood FSH and LH were at menopausal levels, and vaginal maturation index showed 20% to 40% superficial cells. Laparoscopy was performed and streak gonads were seen. Biopsies were taken from each of these for both histologic examination and karyotyping. A karyotype from peripheral blood was also done. Culture of the ovaries was obtained with 17 cells being analyzed, 15 of which were 47,XXX, one of which was 46,XX, and one of which was 45,XO. Chromosome analysis of 20 peripheral leukocytes showed 11 to be 45,XO and nine to be 47,XXX. The patient was considered to be female with mosaicism and has subsequently been treated with replacement estrogen-progestin medication. She experiences regular episodes of withdrawal bleeding while taking this medication.

Case 2. A 26-year-old woman, gravida 0, experienced breast development at age 12, had two spontaneous menses at age 15, and had only intermittent vaginal spotting since then. On examination, there was a small amount of facial hair on the upper lip, normal breast development, and normal pelvic structures. There was abundant cervical mucus. Urinary 17-ketosteroid levels were 11.5 mg/24 hours, maturation index was 0/10/90, serum FSH level was 124 mIU/ml, and serum LH level was 74 mIU/ml. One month later, there was withdrawal bleeding following oral medroxyprogesterone, 10 mg daily for 5 days. At this time, the serum FSH level was 92 mIU/ml and two urinary total pituitary gonadotropin assays had values of between 16 and 50 muu/24 hours. Two months after the progestin-induced withdrawal bleeding, there was spontaneous bleeding for 5 days.

The patient was hospitalized 2 months after the spontaneous bleeding, and at this time there was no cervical mucus. Maturation index was 30/70/0, serum FSH level was 207 mIU/ml, and serum LH level was 72 mIU/ml. Total urine gonadotropins were over 100 muu/24 hours on two different occasions. Total urinary estrogen was 12 mcg/24 hours. Chorionic gonadotropin was undetectable by beta-subunit radioimmunoassay, done through the courtesy of Dr. C. B. Hammond of Duke University, Durham, North Carolina. Laparoscopic visualization and biopsy of the ovaries were done. The right ovary appeared to be a wide streak whereas the left ovary appeared to be a small ovary with a follicle on its surface, and histologic examination of both showed ovarian tissue containing a corpus luteum (Fig. 1).

After the patient received ethinyl estradiol, 0.1 mg daily for 3 weeks, the serum FSH level fell to 20 and LH level to 22 mIU/ml.

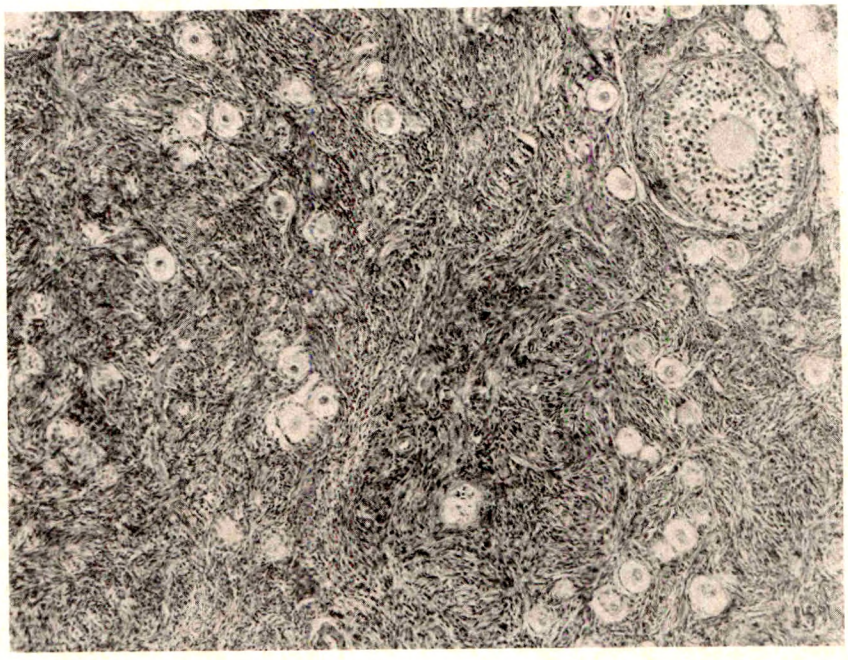


Fig. 2. Ovarian tissue from Case 3 obtained by laparoscopic biopsy. Note normal ovarian tissue with many primary ova and an early developing follicle. (Hematoxylin and eosin. Original magnification ×100.)

Since her initial hospitalization, the patient has had recurrence of abundant clear mucus on several occasions, and at these times the serum FSH level has been 98 and 97 mIU/ml and the serum LH value has been 66 and 93 mIU/ml. Once when there was abundant mucus, human chorionic gonadotropin, 10,000IU, was administered intramuscularly, without producing evidence of ovulation.

Three years after the initial investigation, the patient experienced another episode of spontaneous vaginal bleeding.

Case 3. A 22-year-old woman, gravida 0, experienced menarche at age 13 and had regular menses until oral contraceptive tablets were begun at age 20. She discontinued this medication after 13 months and had no subsequent spontaneous vaginal bleeding. The last episode of withdrawal bleeding had occurred 15 months prior to the patient's first visit.

Approximately 6 months prior to the first visit, the patient developed weakness when climbing stairs and actually fell while going downstairs and also while climbing into a car. She also reported weakness when brushing her teeth and combing and washing her hair at night and increased fatigue in the evenings. She had bilateral ptosis and diplopia. Neuromuscular electrical studies disclosed a decrement in the evoked compound action potential with supramaximal repetitious stimulation of the median nerve; this decrement was corrected following intravenous edrophonium chloride, confirming the presence of neuromuscular blockade consistent with myasthenia gravis.

The thyroid was normal to palpation, and there were no stigmas of Addison's disease. Pelvic examination disclosed moderately atrophic vaginal mucosa, a normal cervix and uterus, and no adnexal masses. Laparoscopic examination demonstrated two small atrophic ovaries, and ovarian biopsy was performed. Histology is shown in Fig. 2. The patient was subsequently treated with estrogens for 3 of each 4 weeks with medroxyprogesterone added during the last 5 treatment days. Withdrawal bleeding occurred. She was also given pyridostigmine bromide for the treatment of myasthenia gravis.

Comment

Associated with normal menopause, there is a gradual loss of primordial ova and follicles, and the ovarian stromal cell nuclei shrink, with fibrous tissue becoming more abundant. In the age group 45 to 49 years, some small follicular cysts and some mild cortical stromal hyperplasia are usually present. The ovary may seem to be formed almost entirely of stroma. After age 50, there is rarely any evidence of follicular activity, and the ovarian cortex is distinguished with difficulty from fibrous tissue elsewhere in the body.[7]

On histologic examination, the ovaries of all but two of the eight patients studied here showed changes typi-

cal of those found in women who had undergone menopause after age 40. There were few or no primordial ova and follicles, along with a compact stroma. Two exceptions in this series are Cases 2 and 3. In both cases, the histology was normal, with a corpus luteum or a developing follicle and ova being identified.

Case 1 is an example of chromosome mosaicism associated with premature menopause. In 1959, Jacobs and associates[8] reported the first case of the 47,XXX syndrome. This particular patient, in addition to mental retardation, had premature menopause at age 19, confirmed by elevated urinary gonadotropins and ovarian biopsy. Other phenotypically female subjects with 47,XXX karyotypes were subsequently studied; the coexistence of premature menopause has proved to be rare, and many patients actually have normal fertility.[9] Gordon and Paulsen[10] reported a single case of premature menopause in XO/XX/XXX/XXXXX mosaicism. Their patient had the onset of menopause at age 17, and the above mosaic was identified in peripheral blood. Attempts to culture ovarian cells were unsuccessful, but they did identify nuclei with zero, one, and two sex chromatin masses in the ovary, suggesting that at least an XX/XXX mosaic existed here. In our Case 1, XO/XX/XXX mosaicism existed with a predominance of XXX in the ovary. Our patient had ovaries which grossly resembled the streak gonads of ovarian agenesis, but she had experienced one spontaneous menses, and a developing follicle was visualized on histologic examination of the ovary. When gonadal abnormality is present in these women with excess X chromosomes, it occurs after ovarian differentiation with some degree of ovarian function possible, and the patient later experiences secondary amenorrhea or premature menopause.[9]

Case 2 is probably an example of the "gonadotropin-resistant ovary syndrome," which was initially described in association with primary amenorrhea.[11] Criteria for diagnosis include endogenous hypergonadotropinemia, presence of normal ovarian follicles, and resistance of ovaries to excessive stimulation with exogenous human gonadotropins. Starup and associates[12] described two patients with secondary amenorrhea, well-developed secondary sex characteristics, and normal 46/XX karyotypes with elevated urinary excretion of FSH and LH, along with normal development of ovarian primordial follicles. A single case was reported by Konickx and Brosens.[13] Efforts to stimulate these ovaries with menopausal gonadotropin plus chorionic gonadotropin were unsuccessful. Our Case 2 is similar to these, but we did not attempt excessive ovarian stimulation with exogenous human gonadotropins except to give human chorionic gonadotropin on one occasion.

The "gonadotropin-resistant ovary syndrome" may be due to an inhibitor that prevents hormone action or to nonresponsiveness of the target cells.[11, 13] Patients with this condition are potentially treatable since follicles are present, and Shangold and associates[14] described one patient who was resistant to stimulation by gonadotropins but who subsequently conceived while receiving estrogenic medication.

Case 3 was associated with myasthenia gravis, and it has been suggested that an autoimmune mechanism is involved in the pathogenesis of this disease.[15] Irvine and associates[16] found antibodies reactive with the theca interna of ovary and with the adrenal cortex in five women with idiopathic adrenal insufficiency and either complete failure of menstruation or premature menopause. This caused them to speculate that ovarian failure may be part of a polyendocrinopathy of which Addison's disease is a part and which is characterized by the formation of autoantibodies. Since autoantibodies have been implicated in premature menopause associated with adrenal insufficiency as well as with myasthenia gravis, we searched for autoantibodies in Case 3 as well as in all other cases. As none was found against theca interna or other normal ovarian tissue, this case may also be an instance of the "gonadotropin-resistant ovary syndrome." Whether or not autoantibodies play a part in the etiology of this condition remains unknown.

In a small group of eight young women with secondary amenorrhea and high FSH levels, only five had findings of typical premature menopause due to ovarian failure with follicular atresia and irreversible sterility. Three women had other conditions, at least two of which are compatible with subsequent pregnancy if appropriate treatment methods can be developed. The possibility of the existence of conditions other than primary ovarian follicular atresia should be investigated, therefore, in young women who have secondary amenorrhea and elevated FSH levels in blood or urine.

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Discussion

Dr. Francis G. Griffin, Virginia Beach, Virginia. (Official Guest) Dr. Board and colleagues have presented eight cases of premature ovarian failure. The first five cases are grouped together as primary follicular atresia, a process during which the vast majority of ova die before reaching full maturation. The ovaries contain about 6 million primordial follicles during the twentieth week of gestation, about 1 to 2 million at birth, and about 400,000 follicles at puberty. There is apparently some inherent mechanism of atresia that starts with formation of the ovary in the fetus and continues until the menopause. It is suggested that premature ovarian failure could result from: (1) unsuspected disease process with destruction of the ovaries, (2) increased utilization of follicles due to increased pituitary overactivity, and (3) congenital small ovaries with decreased primordial follicules. It is fair to assume that all ovaries of women do not contain the same number of primordial follicles; therefore, women having ovaries with decreased follicles with normal atretic rates will experience premature menopause prior to the age of 40.

There has been no evidence presented to suggest the mechanism of follicular atresia, which is the most common ovarian change seen in premature menopause. Until we understand the mechanism of the follicular atresia, the etiology of premature menopause in this group will remain an enigma.

The first case presented in detail is that of a young woman with premature ovarian failure associated with chromosomal mosaicism. In 1959, Jacobs and associates[1] presented a case of a female subject with chromosome triploid XXX, termed "super female," and Gordon and Paulsen[2] presented a case of sex chromosomal mosaicism with four stem cell lines XO/XX/XXX/XXXXX. They explained this by simple terms of nondisjunction in two episodes in the postzygotic period. Both of these patients manifested premature menopause.

When injury to the gonad occurs prior to differentiation the patient will appear phenotypically female but will lack pubertal development. These patients will have a sex chromosomal pattern of X/O. The patient of the case presented had developed secondary sexual characteristics but menstruated only at age 18. When injury to the gonad occurs after differentiation into the ovary, these patients appear to be phenotypically female with secondary sexual characteristics and may have normal fertility. The sex chromosomal pattern is one of triploid X−. Depending on the extent of the ovarian injury, the total number of follices are reduced and with the normal atretic rate ovarian failure is manifested at an earlier age. These patients have high gonadotropin levels symptoms of menopause and the ovaries exhibit an afollicular pattern with hypocellular ovarian stroma, rare corpus albicans, and no mature follicles.

It is essential that chromosome analysis be performed in these patients with "spontaneous premature menopause" in order to identify the role of sex chromosomal abnormalities in the pathogenesis of this entity.

Case 2 represents a 26-year-old woman, gravida 0, with the "gonadotropin-resistant ovary syndrome," which was initially described in 1969 by Jones and associates[3] and includes primary amenorrhea, hypergonadotropinemia, and normal follicular apparatus. In 1972, Van Campenhout and associates[4] defined the "resistant ovarian syndrome," as it is known, by the following characteristics: (1) endogenous hypergonadotropinemia, (2) presence of normal ovarian follicles, and (3) hyporeceptivity of the ovaries to excessive stimulation with exogenous human gonadotropins. This young woman had normal secondary sexual characteristics, infrequent episodes of vaginal bleeding,

high gonadotropin levels, and a normal follicular apparatus. She was stimulated with only human chorionic gonadotropins, 10,000 IU, without evidence of ovulation or menstruation.

As our knowledge of the hypothalamic-pituitary-ovarian axis expands, it is apparent the function cannot be explained in simple terms of a positive and negative feedback. It cannot be assumed in the presence of gonadotropins in the menopausal range with an intact follicular apparatus that hypergonadotropinemia is prima facie evidence of ovarian failure. There have been 11 cases of insensitive ovary syndrome previously reported, revealing only primordial follicles with some developing to the antrum stage. As reported by Goldenberg and associates,[5] the first state of follicular development (to the stage of primordial follicle) does not appear to be dependent on gonadotropin stimulation. Development beyond the primordial follicle, however, seems to be dependent on the availability of FSH and LH. Just how the ovary becomes "sensitized" so that it can respond to gonadotropins is unknown. It appears endogenous and exogenous stimulation with gonadotropins is greater when estrogen levels are, high as demonstrated by work of Bradbury[6] and Kullander.[7] Three patients have been described in the literature with gonadotropin resistant ovaries who later conceived while receiving exogenous estrogens.

It is of interest that patients reported by Shapiro and Rubin.[8] Polansky and DePapp,[9] and Shangold and associates,[10] conceived while taking exogenous estrogens after the ovaries had shown marked resistance to exogenous gonadotropin therapy. It appears estrogens might have something to do with gonadotropin receptor sites in the ovary.

It has been suggested by Jones[11, 12] that the "insensitive ovary syndrome" might represent FSH-receptor protein defect. This was supported by familial tendency. But this concept is hard to explain since Starup and colleagues[13] reported a case of "insensitive ovary syndrome" developing after a reported pregnancy. However, if this is an acquired defect, normal ovarian function is possible, including pregnancy before onset of this dysfunction.

The third case was of a 22-year-old woman with normal secondary sexual characteristics with regular menstrual periods until age 20, followed by amenorrhea after oral contraceptives were discontinued, with an additional diagnosis of myasthenia gravis, ovarian biopsies revealed a normal follicular apparatus.

There is serologic and histologic evidence that some cases of premature ovarian failure may have an autoimmune basis. Such cases have been associated with idiopathic adrenal insufficiency,[14] and these have been explained immunologically by the sharing of antigens between the adrenal cortex and the ovary, since myasthenia gravis might be considered in the group of diseases that have an autoimmune mechanism as an etiology. This patient, however, did not reveal any autoimmune antibodies.

A number of cases have been presented in the literature with secondary amenorrhea and high gonadotropins, in which the patients have received steroid treatment before the onset of amenorrhea. It is interesting that these patients had no further menstrual periods after discontinuing oral contraceptives. The activity of noxious agents cannot be excluded.

In conclusion, the basic etiology of premature menopause remains unknown. Dr. Board's group has presented several categories of patients who fall into clinical patterns with premature menopause but have offered no new concepts as to the basic etiology of premature ovarian failure. I advocate a thorough investigation of these patients at an early date, particularly laparotomy for ovarian biopsy when fertility is a consideration.

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DR. JAMES D. KITCHIN III, Charlottesville, Virginia. The differential diagnosis of hypergonadotropic hypogonadism includes primary ovarian follicular atresia (menopause), gonadal dysgenesis, gonadotropin-resistant ovary syndrome, and various destructive conditions (castration, autoimmune disease, infiltrative disorders, irradiation, infection). With the exception of menopause and the resistant ovary syndrome, diagnosis is usually suggested by history and associated physical findings.

The report of Dr. Board and colleagues re-emphasizes the necessity of caution in assuming irreversible ovarian follicular atresia in young amenorrheic women with elevated gonadotropins. In cases that appear to be hopeless with regard to future ovarian function and fertility, the important questions are what diagnostic methods are available (and rational) to establish irreversibility with certainty and what, if any, treatment is available.

Goldenberg and associates[1] studied 234 women with primary or secondary amenorrhea and correlated gonadal biopsy findings with measurements of urinary gonadotropins and plasma LH and FSH levels. They concluded that a single plasma FSH value was sufficient to diagnose the presence or absence of ovarian follicles in every case. However, they conceded that women with the resistant ovary syndrome[2] may prove exceptions to this conclusion. This condition, also known as the Savage syndrome,[2] has now been reported in women with primary amenorrhea[2-6] as well as with secondary amenorrhea[7-12] and may be related to an abnormality or deficiency of FSH receptor protein,[14] although earlier successful pregnancies in at least two patients suggest that such a defect may be acquired.

Although the gonadotropin-resistant ovary syndrome is rare, it is the probable diagnosis in two of Dr. Board's patients and it is the most important differential diagnosis because ovarian follicles are present and fertility potential exists. One of the original patients of Jones and deMoraes-Ruehsen[2] ovulated after high dosages of exogenous gonadotropins. Other authors[4-6, 7, 12] have used dosages of menopausal gonadotropins as high as 271 ampules over a period of weeks[12] without ovulation and with little or no increase in estrogen production. Few patients have been exposed to this form of therapy and additional data would be desirable if for no other reason than to rule out the theoretical possibility of biologically abnormal endogenous gonadotropin.

At least four successful pregnancies[7, 9-11] have been reported in women with a diagnosis of resistant ovary syndrome and it is intriguing that in each case pregnancy occurred either during estrogen replacement therapy or shortly after it had been discontinued. Suggested mechanisms include: (1) a rebound effect on endogenous gonadotropin levels following suppression and (2) an estrogen enhancement of follicular response to FSH or an increased content of receptor for both FSH and LH.[9]

It is doubtful that extensive diagnostic testing of hypergonadotropic, hypogonadal women is indicated if fertility is not a consideration. However, if a pregnancy is desired or if a definitive diagnosis is required the question is not whether to perform biopsy of the gonads but whether laparoscopic biopsy is adequate. Sutton[13] has presented convincing data to support the contention that laparoscopic ovarian biopsy is not necessarily representative of the histologic structure of the whole ovary and that the procedure is not free of hazard. In the patients reported by Shangold and associates[7] and Polansky and DePapp[10] no follicles were seen on the laparoscopic ovarian biopsy specimen although both later conceived.

The association of hirsutism and the resistant ovary syndrome as noted in Case 2, has been reported previously.[8, 12] Kim[8] suggested that the slight elevation of plasma androgens in his patient could be related to a relative resistance of the follicular compartments to gonadotropic stimulation but a normal or hyperactive stromal response.

I congratulate the authors for this succinct contribution to the expanding literature on primary ovarian failure. In view of current uncertainties regarding specific diagnosis of disorders within this category and because of prognostic implications and connotations of the term "premature menopause" I would like to suggest that "primary ovarian failure" is more suitable. I would also like to ask Dr. Board the following questions.

1. Was the family history helpful in any of these patients? Jones[14] has reported a familial tendency in the resistant ovary syndrome.
2. Are the patients reported currently on a regimen of estrogen-progestin replacement treatment?
3. How many of the eight women have ever tried to conceive? Apparently five of them had menses for 4 to 14 years. Since only one had ever been pregnant (with a subsequent abortion), does this imply that women subject to premature ovarian failure are relatively infertile as a group?

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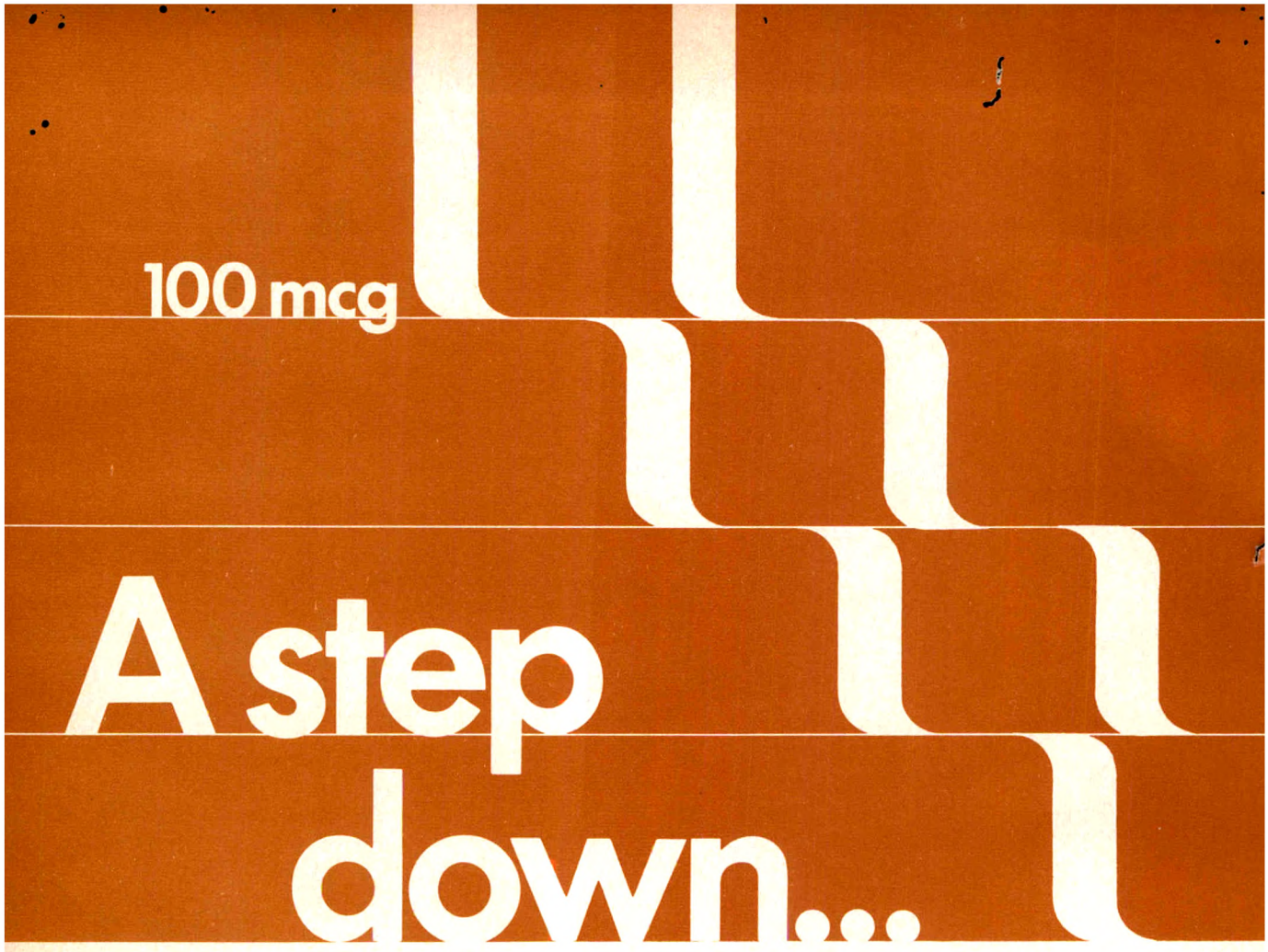
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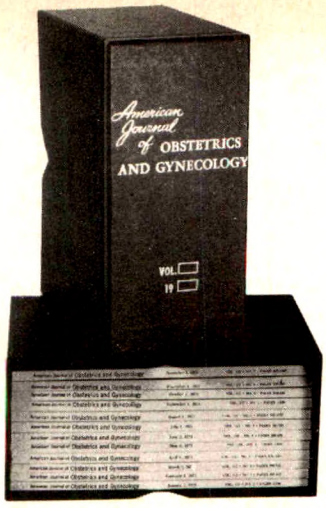
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IMPORTANT NOTE—This information is a BRIEF SUMMARY of the complete prescribing information provided with the product and therefore should not be used as the basis for prescribing the product. This summary was prepared by deleting from the complete prescribing information certain text, tables, and references. The physician should be thoroughly familiar with the complete prescribing information and patient information before prescribing the product.

INDICATION: CONTRACEPTION. The pregnancy rate in women using conventional combination oral contraceptives (containing 35 mcg or more of ethinyl estradiol or 50 mcg or more of mestranol) is generally reported as less than one pregnancy per 100 woman-years of use. Slightly higher rates (somewhat more than one pregnancy per 100 woman-years of use) are reported for some combination products containing 35 mcg or less of ethinyl estradiol, and rates on the order of three pregnancies per 100 woman-years are reported for the progestogen-only oral contraceptives. Table 1 gives ranges of pregnancy rates reported in the literature for other means of contraception. The efficacy of these means of contraception (except the IUD) depends upon the degree of adherence to the method.

Table 1: Pregnancies Per 100 Women-Years. IUD, less than 1-6; Diaphragm with spermicidal product (creams or jellies), 2-20; Condom, 3-36; Aerosol foams, 2-29; Jellies and creams, 4-36; Periodic abstinence (rhythm) all types, less than 1-47; 1. Calendar method, 14-47; 2. Temperature method, 1-20; 3. Temperature method—intercourse only in postovulatory phase, less than 1-7; 4. Mucus method, 1-25; No contraception, 60-80. **DOSE-RELATED RISK OF THROMBOEMBOLISM FROM ORAL CONTRACEPTIVES:** Two studies have shown a positive association between the dose of estrogens in oral contraceptives and the risk of thromboembolism. For this reason, it is prudent and in keeping with good principles of therapeutics to minimize exposure to estrogen. The oral contraceptive product prescribed for any given patient should be that product which contains the least amount of estrogen that is compatible with an acceptable pregnancy rate and patient acceptance. It is recommended that new acceptors of oral contraceptives be started on preparations containing .05 mg or less of estrogen. **CONTRAINDICATIONS:** Oral contraceptives should not be used in women with any of the following conditions: 1. Thrombophlebitis or thromboembolic disorders. 2. A past history of deep vein thrombophlebitis or thromboembolic disorders. 3. Cerebral vascular or coronary artery disease. 4. Known or suspected carcinoma of the breast. 5. Known or suspected estrogen-dependent neoplasia. 6. Undiagnosed, abnormal genital bleeding. 7. Known or suspected pregnancy (see WARNINGS, No. 5).

WARNINGS

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.
The use of oral contraceptives is associated with increased risk of several serious conditions including thromboembolism, stroke, myocardial infarction, hepatic adenoma, gallbladder disease, hypertension. Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks.

1. THROMBOEMBOLIC DISORDERS AND OTHER VASCULAR PROBLEMS. An increased risk of thromboembolic and thrombotic disease associated with the use of oral contraceptives is well established. Four principal studies in Great Britain and three in the United States have demonstrated an increased risk of fatal and nonfatal venous thromboembolism and stroke, both hemorrhagic and thrombotic. These studies estimate that users of oral contraceptives are 4 to 11 times more likely than nonusers to develop these diseases without evident cause. Overall excess mortality due to pulmonary embolism or stroke is on the order of 1.0 to 3.5 deaths annually per 100,000 users and increases with age. **CEREBROVASCULAR DISORDERS:** In a collaborative American study of cerebrovascular disorders in women with and without predisposing causes, it was estimated that the risk of hemorrhagic stroke was 2.0 times greater in users than in nonusers and the risk of thrombotic stroke was 4.0 to 9.5 times greater in users than in nonusers.

MYOCARDIAL INFARCTION: An increased risk of myocardial infarction associated with the use of oral contraceptives has been reported confirming a previously suspected association. These studies, conducted in the United Kingdom, found, as expected, that the greater the number of underlying risk factors for coronary artery disease (cigarette smoking, hypertension, hypercholesterolemia, obesity, diabetes, history of preeclamptic toxemia), the higher the risk of developing myocardial infarction, regardless of whether the patient was an oral contraceptive user or not. Oral contraceptives, however, were found to be a clear additional risk factor. The annual excess case rate (increased risk) of myocardial infarction (fatal and nonfatal) in oral contraceptive users was estimated to be approximately 7 cases per 100,000 women users in the 30-39 age group and 67 cases per 100,000 women users in the 40-44 age group. In terms of relative risk, it has been estimated that oral contraceptive users who do not smoke (smoking is considered a major predisposing condition to myocardial infarction) are about twice as likely to have a fatal myocardial infarction as nonusers who do not smoke. Oral contraceptive users who are also smokers have about a 5-fold increased risk of fatal infarction compared to users who do not smoke, but about a 10-to 12-fold increased risk compared to nonusers who do not smoke. Furthermore, the amount of smoking is also an important factor. In determining the importance of these relative risks, however, the baseline rates for various age groups must be given serious consideration. The importance of other predisposing conditions mentioned above in determining relative and absolute risks has not as yet been quantified; it is quite likely that the same synergistic action exists, but perhaps to a lesser extent. **Risk of Dose:** In an analysis of data derived from several national adverse reaction reporting systems, British investigators concluded that the risk of thromboembolism including coronary thrombosis is directly related to the dose of estrogen used in oral contraceptives. Preparations containing 100 mcg or more of estrogen were associated with a higher risk of thromboembolism than those containing 50-80 mcg of estrogen. Their analysis did suggest, however, that the quantity of estrogen may not be the sole factor involved. This finding has been confirmed in the United States. Careful epidemiological studies to determine the degree of thromboembolic risk associated with progestogen-only oral contraceptives have not been performed. Cases of thromboembolic disease have been reported in women using these products, and they should not be presumed to be free of excess risk. The risk of thromboembolic and thrombotic disorders, in both users and nonusers of oral contraceptives, increases with age. Oral contraceptives are, however, an independent risk factor for these events. **ESTIMATE OF EXCESS MORTALITY FROM CIRCULATORY DISEASES:** A large prospective study carried out in the United Kingdom estimated the mortality rate per 100,000 women per year from diseases of the circulatory system for users and nonusers of oral contraceptives according to age, smoking habits, and duration of use. The overall excess death rate annually from circulatory diseases for oral contraceptive users was estimated to be 20 per 100,000 (ages 15-34—5/100,000; ages 35-44—33/100,000; ages 45-49—140/100,000), the risk being concentrated in older women, in those with a long duration of use, and in cigarette smokers. It was not possible, however, to examine the interrelationships of age, smoking, and duration of use, nor to compare the effects of continuous versus intermittent use. Although the study showed a 10-fold increase in death due to circulatory diseases in users for five or more years, all of these deaths occurred in women 35 or older. Until larger numbers of women under 35 with continuous use for five or more years are available, it is not possible to assess the magnitude of the relative risk for this younger age group. This study reports that the increased risk of circulatory diseases may persist after the pill is discontinued. Another study published at the same time confirms a previously reported increase of mortality in pill users from cardiovascular disease. The available data from a variety of sources have been analyzed to estimate the risk of death associated with various methods of contraception. The estimates of risk of death for each method include the combined risk of the contraceptive method (e.g., thromboembolic and thrombotic disease in the case of oral contraceptives) plus the risk attributable to pregnancy or abortion in the event of method failure. This latter risk varies with the effectiveness of the contraceptive method. The findings of this analysis are shown in Figure 1 below. The study concluded that the mortality associated with all methods of birth control is low and below that associated with childbirth, with the exception of oral contraceptives in women over 40 who smoke. (The rates given for pill only/smokers for each age group are for smokers as a class. For "heavy" smokers [more than 15 cigarettes a day], the rates given would be about double; for "light" smokers [less than 15 cigarettes a day], about 50 percent.) The mortality associated with oral contraceptive use in nonsmokers over 40 is higher than with any other method of contraception in that age group. The lowest mortality is associated with the condom or diaphragm backed up by early abortion. The risk of thromboembolic and thrombotic disease associated with oral contraceptives increases with age after approximately age 30 and, for myocardial infarction, is further increased by hypertension, hypercholesterolemia, obesity, diabetes, or history of preeclamptic toxemia and especially by cigarette smoking. The risk of myocardial infarction in oral contraceptive users is substantially increased in women age 40 and over, especially those with other risk factors. Based on the data currently available, the following chart gives a gross estimate of the risk of death from circulatory disorders associated with the use of oral contraceptives:

SMOKING HABITS AND OTHER PREDISPOSING CONDITIONS—RISK ASSOCIATED WITH USE OF ORAL CONTRACEPTIVES

Age	Below 30	30-39	40+	
Heavy smokers	C	B	A	A—Use associated with very high risk.
Light smokers	D	C	B	B—Use associated with high risk.
Nonsmokers (no predisposing conditions)	D	C,D	C	C—Use associated with moderate risk.
Nonsmokers (other predisposing conditions)	C	C,B	B,A	D—Use associated with low risk.

The physician and the patient should be alert to the earliest manifestations of thromboembolic and thrombotic disorders (e.g., thrombophlebitis, pulmonary embolism, cerebrovascular insufficiency, coronary occlusion, retinal thrombosis, and mesenteric thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately. A four- to six-fold increased risk of postsurgery thromboembolic complications has been reported in oral contraceptive users. If feasible, oral contraceptives should be discontinued at least four weeks before surgery of a type associated with an increased risk of thromboembolism or prolonged immobilization. 2. OCULAR LESIONS. There have been reports of neuro-ocular lesions such as optic neuritis or retinal thrombosis associated with the use of oral contraceptives. Discontinue oral contraceptive medication if there is unexplained, sudden or gradual, partial or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal vascular lesions and institute appropriate diagnostic and therapeutic measures. 3. CARCINOMA. Long-term continuous administration of either natural or synthetic estrogen in certain animal species increases the frequency of carcinoma of the breast, cervix, vagina, and liver. Certain synthetic progestogens, none currently contained in oral contraceptives, have been noted to increase the incidence of mammary nodules, benign and malignant, in dogs. In humans, three case control studies have reported an increased risk of endometrial carcinoma associated with the prolonged use of exogenous estrogen in postmenopausal women. One publication reported on the first 21 cases submitted by physicians to a registry of cases of adenocarcinoma of the endometrium in women under 40 on oral contraceptives. Of the cases found in women without predisposing risk factors for adenocarcinoma of the endometrium (e.g., irregular bleeding at the time oral contraceptives were first given, polycystic ovaries), nearly all occurred in women who had used a sequential oral contraceptive. These products are no longer marketed. No evidence has been reported suggesting an increased risk of endometrial cancer in users of conventional combination or progestogen-only oral contraceptives. Several studies have found no increases in breast cancer in women taking oral contraceptives or estrogens. One study, however, while also noting no overall increased risk of breast cancer in women treated with oral contraceptives, found an excess risk in the subgroups of oral contraceptive users with documented benign breast disease. A reduced occurrence of benign breast tumors in users of oral contraceptives has been well-documented. In summary, there is at present no confirmed evidence from human studies of an increased risk of cancer associated with oral contraceptives. Close clinical surveillance of all women taking oral contraceptives is, nevertheless, essential. In all cases of undiagnosed persistent or recurrent abnormal vaginal bleed-

Figure 1: Estimated annual number of deaths associated with control of fertility and no control per 100,000 nonsmoking women, by regimen of control and age of woman.

	15-19	20-24	25-29	30-34	35-39	40-44
No method	5.5	5.2	7.1	14.0	19.3	21.9
Abortion only	2.3	2.5	2.5	5.2	9.8	6.6
Pill only-nonsmokers	1.3	1.4	1.4	2.2	4.5	3.1
Pill only-smokers	1.5	1.6	1.6	10.8	13.4	58.9
IUDs only	1.1	1.2	1.2	1.4	1.6	1.4
Traditional contraception only	1.1	1.4	1.9	3.7	4.7	4.0
Traditional contraception and abortion	0.3	0.4	0.4	0.8	1.4	0.8

4. HEPATIC TUMORS. Benign hepatic adenomas have been found to be associated with the use of oral contraceptives. One study showed that oral contraceptive formulations with high hormonal potency were associated with a higher risk than lower potency formulations. Although benign, hepatic adenomas may rupture and may cause death through intra-abdominal hemorrhage. This has been reported in short-term as well as long-term users of oral contraceptives. Two studies relate risk with duration of use of the contraceptive, the risk being much greater after four or more years of oral contraceptive use. While hepatic adenoma is a rare lesion, it should be considered in women presenting abdominal pain and tenderness, abdominal mass or shock. A few cases of hepatocellular carcinoma have been reported in women taking oral contraceptives. The relationship of these drugs to this type of malignancy is not known at this time. 5. USE IN OR IMMEDIATELY PRECEDING PREGNANCY, BIRTH DEFECTS IN OFFSPRING, AND MALIGNANCY IN FEMALE OFFSPRING. The use of female sex hormones—both estrogenic and progestational agents—during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a nonsteroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare. This risk has been estimated to be on the order of 1 to 4 in 1000 exposures. Although there is no evidence at the present time that oral contraceptives further enhance the risk of developing this type of malignancy, such patients should be monitored with particular care if they elect to use oral contraceptives instead of other methods of contraception. Furthermore, a high percentage of such exposed women (from 30 to 90%) have been found to have epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether this condition is a precursor of vaginal malignancy. Male children so exposed may develop abnormalities of the urogenital tract. Although similar data are not available with the use of other estrogens, it cannot be presumed that they would not induce similar changes. An increased risk of congenital anomalies, including heart defects and limb defects, has been reported with the use of sex hormones, including oral contraceptives, in pregnancy. One case control study has estimated a 4.7-fold increase in risk of limb-reduction defects in infants exposed in utero to sex hormones (oral contraceptives, hormonal withdrawal tests for pregnancy or attempted treatment for threatened abortion). Some of these exposures were very short and involved only a few days of treatment. The data suggest that the risk of limb-reduction defects in exposed fetuses is somewhat less than one in 1,000 live births. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well-controlled studies that progestogens are effective for these uses. There is some evidence that triploidy and possibly other types of polyploidy are increased among abortuses from women who become pregnant soon after ceasing oral contraceptives. Embryos with these anomalies are virtually always aborted spontaneously. Whether there is an overall increase in spontaneous abortion of pregnancies conceived soon after stopping oral contraceptives is unknown. It is recommended that for any patient who has missed two consecutive periods, pregnancy should be ruled out before continuing the contraceptive regimen. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at the time of the first missed period (or after 45 days from the last menstrual period if the progestogen-only oral contraceptives are used), and further use of oral contraceptives should be withheld until pregnancy has been ruled out. If pregnancy is confirmed, the patient should be apprised of the potential risks to the fetus and the advisability of continuation of the pregnancy should be discussed in the light of these risks. It is also recommended that women who discontinue oral contraceptives with the intent of becoming pregnant use an alternate form of contraception for a period of time before attempting to conceive. Many clinicians recommend three months although no precise information is available on which to base this recommendation. The administration of progestogen-only or progestogen-estrogen combinations to induce withdrawal bleeding should not be used as a test of pregnancy. 6. GALLBLADDER DISEASE. Studies report an increased risk of surgically confirmed gallbladder disease in users of oral contraceptives and estrogens. In one study, an increased risk appeared after two years of use and doubled after four or five years of use. In one of the other studies, an increased risk was apparent between six and twelve months of use. 7. CARBOHYDRATE AND LIPID METABOLIC EFFECTS. A decrease in glucose tolerance has been observed in a significant percentage of patients on oral contraceptives. For this reason, prediabetic and diabetic patients should be carefully observed while receiving oral contraceptives. An increase in triglycerides and total phospholipids has been observed in patients receiving oral contraceptives. The clinical significance of this finding remains to be defined. 8. ELEVATED BLOOD PRESSURE. An increase in blood pressure has been reported in patients receiving oral contraceptives. In some women hypertension may occur within a few months of beginning oral contraceptive use. In the first year of use, the prevalence of women with hypertension is low in users and may be no higher than that of a comparable group of nonusers. The prevalence in users increases, however, with longer exposure, and in the fifth year of use is two and a half to three times the reported prevalence in the first year. Age is also strongly correlated with the development of hypertension in oral contraceptive users. Women who previously have had hypertension during pregnancy may be more likely to develop elevation of blood pressure when given oral contraceptives. Hypertension that develops as a result of taking oral contraceptives usually returns to normal after discontinuing the drug. 9. HEADACHE. The onset or exacerbation of migraine or development of headache of a new pattern which is recurrent, persistent, or severe, requires discontinuation of oral contraceptives and evaluation of the cause. 10. BLEEDING IRREGULARITIES. Breakthrough bleeding, spotting, and amenorrhea are frequent reasons for patients discontinuing oral contraceptives. In breakthrough bleeding, as in all cases of irregular bleeding from the vagina, nonfunctional causes should be borne in mind. In undiagnosed persistent or recurrent abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy. If pathology has been excluded, time or a change to another formulation may solve the problem. Changing to an oral contraceptive with a higher estrogen content, while potentially useful in minimizing menstrual irregularity, should be done only if necessary since this may increase the risk of thromboembolic disease. Women with a past history of oligomenorrhea or secondary amenorrhea or young women without regular cycles may have a tendency to remain anovulatory or to become amenorrheic after discontinuation of oral contraceptives. Women with these preexisting problems should be advised of this possibility and encouraged to use other contraceptive methods. Postuse anovulation, possibly prolonged, may also occur in women without previous irregularities. 11. ECTOPIC PREGNANCY. Ectopic as well as intrauterine pregnancy may occur in contraceptive failures. 12. BREAST FEEDING. Oral contraceptives given in the postpartum period may interfere with lactation. There may be a decrease in the quantity and quality of the breast milk. Furthermore, a small fraction of the hormonal agents in oral contraceptives has been identified in the milk of mothers receiving these drugs. The effects, if any, on the breast-fed child have not been determined. If feasible, the use of oral contraceptives should be deferred until the infant has been weaned. **PRECAUTIONS: General:** 1. A complete medical and family history should be taken prior to the initiation of oral contraceptives. The pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen and pelvic organs, including Papanicolaou smear and relevant laboratory tests. As a general rule, oral contraceptives should not be prescribed for longer than one year without another physical examination being performed. 2. Under the influence of estrogen-progestogen preparations, preexisting uterine leiomyomata may increase in size. 3. Patients with a history of psychic depression should be carefully observed and the drug discontinued if depression recurs to a serious degree. Patients becoming significantly depressed while taking oral contraceptives should stop the medication and use an alternate method of contraception in an attempt to determine whether the symptom is drug-related. 4. Oral contraceptives may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention, such as convulsive disorders, migraine syndrome, asthma, or cardiac or renal insufficiency. 5. Patients with a past history of jaundice during pregnancy have an increased risk of recurrence of jaundice while receiving oral contraceptive therapy. If jaundice develops in any patient receiving such drugs, the medication should be discontinued. 6. Steroid hormones may be poorly metabolized in patients with impaired liver function and should be administered with caution in such patients. 7. Oral contraceptive users may have disturbances in normal tryptophan metabolism which may result in a relative pyridoxine deficiency. The clinical significance of this is yet to be determined. 8. Serum folate levels may be depressed by oral contraceptive therapy. Since the pregnant woman is predisposed to the development of folate deficiency and the incidence of folate deficiency increases with increasing gestation, it is possible that if a woman becomes pregnant shortly after stopping oral contraceptives, she may have a greater chance of developing folate deficiency and complications attributed to this deficiency. 9. The pathologist should be advised of oral contraceptive therapy when relevant specimens are submitted. 10. Certain endocrine and liver function tests and blood components may be affected by estrogen-containing oral contraceptives: a. Increased sulfobromophthalein retention. b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability. c. Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered. d. Decreased pregnanediol excretion. e. Reduced response to metyrapone test. **INFORMATION FOR THE PATIENT: (See Patient Package Insert). DRUG INTERACTIONS:** Reduced efficacy and increased incidence of breakthrough bleeding have been associated with concomitant use of rifampin. A similar association has been suggested with barbiturates, phenylbutazone, phenytoin sodium, and ampicillin. **CARCINOGENESIS, PREGNANCY, NURSING MOTHERS: See CONTRAINDICATIONS and WARNINGS. ADVERSE REACTIONS:** An increased risk of the following serious adverse reactions has been associated with the use of oral contraceptives (see WARNINGS): Thrombophlebitis. Pulmonary embolism. Coronary thrombosis. Cerebral thrombosis. Cerebral hemorrhage. Hypertension. Gallbladder disease. Liver tumors. Congenital anomalies. There is evidence of an association between the following conditions and the use of oral contraceptives, although additional confirmatory studies are needed: Mesenteric thrombosis. Neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis. The following adverse reactions have been reported in patients receiving oral contraceptives and are believed to be drug-related: Nausea, usually the most common adverse reaction. Vomiting, occurs in approximately 10% or less of patients during the first cycle. Other reactions, as a general rule, are seen much less frequently or only occasionally. Gastrointestinal symptoms (such as abdominal cramps and bloating). Breakthrough bleeding. Spotting. Change in menstrual flow. Dysmenorrhea. Amenorrhea during and after treatment. Temporary infertility after discontinuance of treatment. Edema. Chloasma or melasma which may persist. Breast changes: tenderness, enlargement, and secretion. Change in weight (increase or decrease). Change in cervical erosion and cervical secretion. Possible diminution in lactation when given immediately postpartum. Cholestatic jaundice. Migraine. Increase in size of uterine leiomyomata. Rash (allergic). Mental depression. Reduced tolerance to carbohydrates. Vaginal candidiasis. Change in corneal curvature (steepening). Intolerance to contact lenses. The following adverse reactions have been reported in users of oral contraceptives, and the association has been neither confirmed nor refuted: Premenstrual-like syndrome. Cataracts. Changes in libido. Chorea. Changes in appetite. Cystitis-like syndrome. Headache. Nervousness. Dizziness. Hirsutism. Loss of scalp hair. Erythema multiforme. Erythema nodosum. Hemorrhagic eruption. Vaginitis. Porphyria. Impaired renal function. (ORTHO-NOVUM 1/50□21 and ORTHO-NOVUM 1/50□28 contain tartrazine. Allergic reactions have been reported with the ingestion of this dye in some patients.) **ACUTE OVERDOSE:** Serious ill effects have not been reported following acute ingestion of large doses of oral contraceptives by young children. Overdosage may cause nausea, and withdrawal bleeding may occur in females.

ORTHO

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